Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2017-B-237 Cariprazin

Stand: November 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Cariprazin **[Schizophrenie bei Erwachsenen]** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe II. Zugelassene Arzneimittel im Anwendungsgebiet* *Hinweis:* Es werden keine Wirkstoffe aufgelistet, die für die Behandlung von Unruhe- und Erregungszuständen im Rahmen psychotischer Störungen, aber nicht zur Therapie der Grunderkrankung zugelassen sind.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Psychotherapie kann neben oder nach einer somatisch ärztlichen Behandlung von Krankheiten oder deren Auswirkungen angewandt werden, wenn psychische Faktoren einen wesentlichen pathogenetischen Anteil daran haben und sich ein Ansatz für die Anwendung von Psychotherapie bietet: Indikationen hierfür können nur sein: […] 4. Schizophrene und affektive psychotische Störungen. (§ 26 Abs. 2 Psychotherapie-RL) - Ergotherapie: Psychisch-funktionelle Behandlung und Hirnleistungstraining/neuropsychologisch orientierte Behandlung gemäß Heilmittel-Richtlinie. - Soziotherapie gemäß Soziotherapie-Richtlinie.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss vom 16. April 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Lurasidon
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Cariprazin N05AX15 Reagila®	Reagila wird zur Behandlung von Schizophrenie bei erwachsenen Patienten angewendet.
Fluphenazin N05AB02 Lyogen®	*(oral:)* Fluphenazindihydrochlorid wird angewendet bei: - akuten psychotischen Syndromen mit Wahn, Halluzinationen, Denkstörungen, Denkzerfahrenheit, Ich-Störungen; - katatonen Syndromen; - chronisch verlaufenden endogenen Psychosen (Symptomsuppression und Rezidivprophylaxe); - psychomotorischen Erregungszuständen. *(Depot-Injektionslösung:)* Langzeittherapie und Rezidivprophylaxe schizophrener Psychosen.
Perphenazin N05AB03 Perphenazin-neuraxpharm®	- Endogene Psychosen, z.B. akute und chronische Schizophrenien, insbesondere katatone und akute paranoid-halluzinatorische Formen - Psychomotorische Erregungszustände psychotischer Genese
Perazin N05AB10 Taxilan®	- Akute psychotische Syndrome mit Wahn, Halluzinationen, Denkstörungen, Ich-Störungen; - Katatone Syndrome; - Chronisch verlaufende endogene und exogene Psychosen (zur Symptomsuppression und Rezidivprophylaxe der Schizophrenie); - Maniforme Syndrome; - Psychomotorische Erregungszustände.
Thioridazin N05AC02 Melleril®	Zur Behandlung von Patienten mit chronischen Formen schizophrener und anderer Psychosen, bei denen psychomotorische Unruhe und Erregungszustände im Vordergrund stehen, insbesondere als Alternative oder Begleitmedikation, wenn andere Standardtherapeutika nicht ausreichend wirksam sind.

Haloperidol N05AD01 Haldol-Jansen®	*(oral:)* - Akute und chronische schizophrene Syndrome - Organisch bedingte Psychosen - Akute manische Syndrome - Akute psychomotorische Erregungszustände […] *(Injektionslösung:)* Zur akuten Intervention oder wenn eine orale Therapie nicht möglich ist, bei - akuten und chronischen schizophrenen Syndromen - psychomotorischen Erregungszuständen psychotischer Genese *(Depot-Injektionslösung:)* Erhaltungstherapie und Rezidivprophylaxe bei chronisch schizophrenen und maniformen Zuständen. Haloperidoldecanoat darf nur bei Patienten angewendet werden, bei denen das Ausmaß der therapeutischen Wirksamkeit sowie die Nebenwirkungen einer oralen Therapie bekannt sind und bei denen eine adäquate orale Therapie mit einem Neuroleptikum nicht möglich ist. […]
Bromperidol N05AD06 Impromen®	Akute, subakute und chronische Schizophrenien.
Benperidol N05AD07 Glianimon®	- Akute psychotische Syndrome mit Wahn, Halluzinationen, Denk-Störungen und Ich-Störungen; katatone Syndrome; delirante und andere exogen-psychotische Syndrome - chronisch verlaufende endogene und exogene Psychosen (zur Symptomsuppression) - maniforme Syndrome - psychomotorische Erregungszustände
Sertindol N05AE03 Serdolect®	Sertindol ist für die Behandlung der Schizophrenie angezeigt. Aufgrund kardiovaskulärer Sicherheitsbedenken sollte Sertindol nur bei Patienten angewendet werden, die zumindest ein anderes Antipsychotikum nicht vertragen haben. Sertindol sollte nicht in Notfallsituationen bei akut gestörten Patienten zur raschen Symptomreduktion verabreicht werden.
Ziprasidon N05AE04 Zeldox®	Ziprasidon wird angewendet zur Behandlung der Schizophrenie bei Erwachsenen. […]

Lurasidon N05AE05 Latuda®	Latuda ist für die Behandlung der Schizophrenie bei Erwachsenen ab 18 Jahren indiziert.
Flupentixol N05AF01 Fluanxol®	*(oral:)* Akut- und Langzeitbehandlung schizophrener Psychosen. […] *(2%-Depot-Injektionslösung:)* Langzeitbehandlung und Rezidivprophylaxe schizophrener Psychosen. *(10%-Depot-Injektionslösung:)* Chronische schizophrene Psychosen.
Zuclopenthixol N05AF05 Ciatyl-Z®	*(oral:)* Akute und chronische Schizophrenie […] *(schnellfreisetzende Depot-Injektionslösung:)* Zur Initialbehandlung akuter Psychosen einschließlich Manie und Exazerbationen chronischer Psychosen. *(Depot-Injektionslösung:)* Langzeitbehandlung chronischer Schizophrenien. Ciatyl-Z Depot darf nur bei Patienten angewendet werden, bei denen eine adäquate orale Therapie mit einem Neuroleptikum nicht möglich ist.
Fluspirilen N05AG01 Imap®	Akut produktive und chronisch schizophrene Psychosen (Langzeittherapie und Rezidivprophylaxe).
Pimozid N05AG02 Orap®	Erhaltungstherapie bei chronischen Psychosen des schizophrenen Formenkreises.

Clozapin N05AH02 Leponex®	<u>Therapieresistente Schizophrenie</u> Leponex ist zur Behandlung therapieresistenter Schizophrenie und schizophrener Patienten angezeigt, die mit schweren, nicht zu behandelnden neurologischen unerwünschten Reaktionen auf andere Neuroleptika einschließlich eines atypischen Neuroleptikums reagieren. Therapieresistenz ist definiert als Ausbleiben befriedigender klinischer Besserung trotz Verwendung angemessener Dosen von mindestens zwei verschiedenen Neuroleptika einschließlich eines atypischen Neuroleptikums, die für eine angemessene Dauer verabreicht wurden. […]
Olanzapin N05AH03 Zyprexa®; Zypadhera®	*(oral:)* Olanzapin ist für die Behandlung der Schizophrenie angezeigt. Bei Patienten, die initial auf die Behandlung angesprochen haben, ist Olanzapin bei fortgesetzter Behandlung zur Aufrechterhaltung der klinischen Besserung wirksam. *(Depot-Injektionssuspension:)* Erhaltungstherapie bei erwachsenen Patienten mit Schizophrenie, die während einer akuten Behandlung hinreichend mit oralem Olanzapin stabilisiert wurden.
Quetiapin N05AH04 Seroquel®	Seroquel ist indiziert zur: - Behandlung der Schizophrenie. […]
Sulpirid N05AL01 Dogmatil®	akute und chronische Schizophrenien im Erwachsenen- und Kindesalter […]
Amisulprid N05AL05 Solian®	Solian ist angezeigt für die Behandlung von akuten und chronischen schizophrenen Störungen: - produktive Zustände mit Wahnvorstellungen, Halluzinationen, Denkstörungen, Feindseligkeit, Misstrauen, - primär negative Zustände (Defektsyndrom) mit Affektverflachung, emotionalem und sozialem Rückzug.
Risperidon N05AX08 Risperdal®	*(oral:)* Risperdal ist indiziert zur Behandlung der Schizophrenie. […] *(Depot-Injektionssuspension:)* Risperdal Consta ist indiziert zur Erhaltungstherapie der Schizophrenie bei Patienten, die zurzeit mit oralen Antipsychotika stabilisiert sind.

Aripiprazol N05AX12 Abilify®	*(oral:)* Abilify® wird angewendet für die Behandlung der Schizophrenie bei Erwachsenen und bei Jugendlichen ab 15 Jahren. […] *(Depot-Injektionssuspension:)* Abilify Maintena® wird für die Erhaltungstherapie von Schizophrenie bei erwachsenen Patienten, die stabil mit oral angewendetem Aripiprazol eingestellt wurden, angewendet.
Paliperidon N05AX13 Invega®; Xeplion®; Trevicta®	*(oral:)* Invega ist indiziert zur Behandlung der Schizophrenie bei Erwachsenen und bei Jugendlichen ab 15 Jahre. Invega ist indiziert zur Behandlung von schizoaffektiven Störungen bei Erwachsenen. *(Depot-Injektionssuspension:)* Xeplion wird zur Erhaltungstherapie der Schizophrenie bei erwachsenen Patienten angewendet, die auf Paliperidon oder Risperidon eingestellt wurden. Bei bestimmten erwachsenen Patienten mit Schizophrenie und früherem Ansprechen auf orales Paliperidon oder Risperidon kann Xeplion ohne vorherige Einstellung auf eine orale Behandlung angewendet werden, wenn die psychotischen Symptome leicht bis mittelschwer sind und eine Behandlung mit einem Depot-Antipsychotikum erforderlich ist. Trevicta, eine 3-Monats-Injektion, wird zur Erhaltungstherapie der Schizophrenie bei Erwachsenen angewendet, die klinisch stabil auf die 1-Monats-Injektion Paliperidonpalmitat eingestellt sind (siehe Abschnitt 5.1).

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation Schizophrenie durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 18.10.2017 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1325 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 29 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Schizophrenie bei Erwachsenen

Abkürzungen:

AOM	Aripiprazole once monthly
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BAS	Barnes Akathisia Rating Scale
BPRS	Brief Psychatric Rating Scale
CBT	Brief cognitive behavioural therapy
CGI	Clinical Global Impression
DAHTA	DAHTA-Datenbank
EPS	Extrapyramidal symptoms
ESRS	Extrapyramidal symptom rating scale
FGA	First-generation antipsychotics
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LAI-APs	Long-acting injectable antipsychotics
MD	mean differences
NCCN	National Comprehensive Cancer Network
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
OAP	Oral antipsychotics
OA	Oral Aripiprazole
PANSS	Positive and Negative Syndrome Scale
SLOF	Specific Level of Fuctioning Scale
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

IQWiG, 2017 [12].

Systemische Therapie bei Erwachsenen als Psychotherapie-verfahren

N14-02

Fragestellung/Ziele:

Ziel der vorliegenden Untersuchung ist die Nutzenbewertung der systemischen Therapie als Psychotherapieverfahren

Population:

Erwachsene mit einer psychischen Störung

Endpunkte:

Tabelle 27: Matrix der Endpunkte des Störungsbereichs Schizophrenie und affektive psychotische Störungen

Studie	Endpunkte										
	Morbidität								Allgemeines und soziales Funktionsniveau einschließlich Arbeits- und Erwerbsfähigkeit		
				Schizophrenie-symptomatik							
	Mortalität	Symptomverbesserung manische und depressive Symptomatik	Zeit bis Symptomverbesserung manische und depressive Symptomatik	Schizophreniesymptomatik (Positivskala)	Schizophreniesymptomatik (Negativskala)	Schizophreniesymptomatik (global)	Generelle psychiatrische Symptomatik	Gesundheitsbezogene Lebensqualität	Allgemeines Funktionsniveau	Soziales Funktionsniveau	Unerwünschte Ereignisse
Vergleich systemische Therapie versus Beratung und Informationsvermittlung											
Miller 2004	–	●	●	–	–	–	–	–	–	–	–
Vergleich systemische Therapie versus keine Zusatzbehandlung											
Cao 2007	–	–	–	–	–	●	–	●	–	–	–
Priebe 2015	–	–	–	●	●	–	●	●	–	●	–
Zhang 2006	–	–	–	–	–	●	–	–	●	–	–
Zhou 2003	–	–	–	–	–		●	–	–	–	–
Miller 2004	–	●	●	–	–		–	–	–	–	–
–: keine Daten extrahiert; ●: Daten extrahiert											

Ergebnis /Fazit:

Die Nutzenaussagen in den Störungsbereichen depressive Störungen, Essstörungen sowie **Schizophrenie** und affektive psychotische Störungen beruhen auf Endpunkten zur psychischen Symptomatik sowie zum allgemeinen und sozialen Funktionsniveau.

Vergleich systemische Therapie versus Beratung und Informationsvermittlung

- Hinsichtlich der Endpunkte **Symptomverbesserung manische und depressive Symptomatik** ergibt sich kein Anhaltspunkt für einen Nutzen oder Schaden der systemischen Therapie verglichen mit Beratung und Informationsvermittlung.
- Hinsichtlich der Endpunkte **Mortalität**, **Zeit bis Symptomverbesserung manische und depressive Symptomatik, Schizophreniesymptomatik, generelle psychiatrische Symptomatik, gesundheitsbezogene Lebensqualität, allgemeines Funktionsniveau**

	und **unerwünschte Ereignisse** wird keine Aussage über einen Nutzen oder Schaden der systemischen Therapie im Vergleich zu Beratung und Informationsvermittlung getroffen, da für diese Endpunkte keine Daten oder verwertbaren Ergebnisse vorliegen. **Vergleich systemische Therapie versus keine Zusatzbehandlung** • Hinsichtlich des Endpunkts **Schizophreniesymptomatik (global)** ergibt sich ein Hinweis auf einen Nutzen der systemischen Therapie verglichen mit dem Komparator keine Zusatz-behandlung, basierend auf Ergebnissen zum Auswertungszeitpunkt 2 beziehungsweise 2,5 Jahre. Damit lässt sich hinsichtlich der Endpunktkategorie **Schizophreniesymptomatik** ein Hinweis auf einen Nutzen der systemischen Therapie verglichen mit dem Komparator keine Zusatzbehandlung feststellen. Hinsichtlich des Endpunkts **allgemeines Funktionsniveau** ergibt sich ein Anhaltspunkt für einen Nutzen der systemischen Therapie verglichen mit dem Komparator keine Zusatzbehandlung. Dieser beruht auf dem Auswertungszeitpunkt 2,5 Jahre. • Hinsichtlich der Endpunkte **Symptomverbesserung manische und depressive Symptomatik, generelle psychiatrische Symptomatik, gesundheitsbezogene Lebensqualität** und **soziales Funktionsniveau** ergibt sich kein Anhaltspunkt für einen Nutzen oder Schaden der systemischen Therapie verglichen mit dem Komparator keine Zusatzbehandlung. • Hinsichtlich der Endpunkte **Mortalität, Zeit bis Symptomverbesserung manische und depressive Symptomatik** und **unerwünschte Ereignisse** wird keine Aussage über einen Nutzen oder Schaden der systemischen Therapie im Vergleich zu dem Komparator keine Zusatzbehandlung getroffen, da für **Ergebnis: Störungsbereich Schizophrenie und affektive psychotische Störungen** In der Gesamtschau von 5 Studien mit verwertbaren Daten im Störungsbereich Schizophrenie und affektive psychotische Störungen ergibt sich ein Hinweis auf einen Nutzen der systemischen Therapie im Vergleich zum Komparator keine Zusatzbehandlung. In keinem der hier betrachteten Vergleiche lagen dabei Daten für die Endpunkte Mortalität und unerwünschte Ereignisse vor.
G-BA, 2016 [6]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – **Lurasidon** **Siehe auch: IQWiG, 2015 [11].**	**Fazit:** **a) Akuttherapie von Patienten mit Schizophrenie** • <u>Zweckmäßige Vergleichstherapie:</u> Amisulprid oder Aripiprazol oder Olanzapin oder Paliperidon oder Quetiapin oder Risperidon oder Ziprasidon. • <u>Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:</u> *Zusatznutzen ist nicht belegt.* **b) Rückfallprophylaxe bei Patienten mit Schizophrenie** • <u>Zweckmäßige Vergleichstherapie:</u> Amisulprid oder Aripiprazol oder Olanzapin oder Paliperidon oder Quetiapin oder Risperidon oder Ziprasidon. • <u>Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Risperidon:</u> *Zusatznutzen ist nicht belegt.*

G-BA, 2016 [7]. Richtlinie des Gemeinsamen Bundesauschusses über die Durchführung der Psychotherapie **(Psychotherapie-Richtlinie)** **in Kraft getreten am 16.02.2017**	**Fazit:** in der Fassung vom 24. November 2016; veröffentlicht im Bundesanzeiger (BAnz AT 15.02.2017 B2); in Kraft getreten am 16.02.2017 Die vom Gemeinsamen Bundesausschuss (G-BA) gemäß § 92 Absatz 6a des Fünften Buches Sozialgesetzbuch (SGB V) beschlossene Richtlinie dient der Sicherung einer den gesetzlichen Erfordernissen entsprechenden ausreichenden, zweckmäßigen und wirtschaftlichen Psychotherapie der Versicherten und ihrer Angehörigen in der vertragsärztlichen Versorgung zu Lasten der Krankenkassen. Zur sinnvollen Verwendung der Mittel ist die folgende Richtlinie zu beachten. Sie dient als Grundlage für Vereinbarungen, die zur Durchführung von Psychotherapie in der vertragsärztlichen Versorgung zwischen den Vertragspartnern abzuschließen sind.
G-BA, 2017 [8]. Richtlinie des Gemeinsamen Bundesausschusses Richtlinie über die Verordnung von Heilmitteln in der vertragsärztlichen Versorgung **(Heilmittel-Richtlinie/HeilM-RL)**	**Fazit:** (1) Heilmittel sind persönlich zu erbringende medizinische Leistungen. 2 Heilmittel sind • die einzelnen Maßnahmen der Physikalischen Therapie (§§ 18 bis 25) • die einzelnen Maßnahmen der Podologischen Therapie (§ 28 Absatz 4 Nummer 1 bis 4) • die einzelnen Maßnahmen der Stimm-, Sprech- und Sprachtherapie (§§ 31 bis 33) • die einzelnen Maßnahmen der Ergotherapie (§§ 36 bis 40) (2) Die Richtlinie regelt die Verordnung von Heilmitteln im Rahmen der vertragsärztlichen Versorgung. Die Verordnung von kurortsspezifischen bzw. ortsspezifischen Heilmitteln ist nicht Gegenstand dieser Richtlinie

Cochrane Reviews

Barber S et al., 2017 [2]. Clozapine combinedwith different antipsychotic drugs for treatment-resistant schizophrenia (Review)	1. Fragestellung To determine the clinical effects of various clozapine combination strategies with antipsychotic drugs in people with treatment-resistant schizophrenia both in terms of efficacy and tolerability. • original search for this review (March and November 2008; the original review included three RCTs) • search update (August 2015)
	2. Methodik Population: treatment-resistant schizophrenia (or related disorders) (e.g. schizoaffective disorder, schizophreniformdisorder) Intervention: clozapine plus another antipsychotic drug Komparator: clozapine plus a different antipsychotic drug Endpunkt: Primäre Endpunkte: *Clinical response* (1.1. No clinically significant response in global state - as defined by each of the studies, 1.2. No clinically significant response in mental state - as defined by each of the studies. *Adverse effect* (2.1. Weight gain); Sekundäre Endpunkte: u.a. 3. Leaving the study early, Hospital admission, Quality of life Suchzeitraum (Aktualität der Recherche): 28 August 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 RCTs (N=209)(Originalrecherche) + 2 RCTs (Updaterecherche) Qualitätsbewertung der Studien: Cochrane Handbook for Systematic Reviews of Interventions
	3. Ergebnisdarstellung Eingeschlossene Studien: - clozapine plus aloperidol vs. clozapine plus aripiprazole. - clozapine plus amisulpride vs. clozapine plus quetiapine. - clozapine plus risperidone vs. clozapine plus sulpiride. - clozapine plus ziprasidone vs. clozapine plus risperidone. - clozapine plus ziprasidone vs. clozapine plus quetiapine. Qualitätsbewertung: The reliability of the evidence is questionable and was noted to be low or very low quality. Only a small number of studies, with limited data were available. No data were available for important measures such as quality of life and service use and no firm conclusions could be made. Hinweis: It was not possible to perform an overall analysis because the five studies were too different. Therefore, all results were based on data from one study per comparison. **Clozapine plus aripiprazole versus clozapine plus haloperidol** no long-term significant difference between aripiprazole and haloperidol combination strategies in change of mental state (1 RCT, n = 105, MD 0.90, 95% CI -4.38 to 6.18, *low quality evidence*). no adverse effect data for weight gain but there was a benefit of aripiprazole for adverse effects measured by the LUNSERS at 12 weeks (1 RCT, n = 105, MD -4.90, 95% CI -8.48 to -1.32) and 24 weeks (1 RCT, n = 105, MD -4.90, 95% CI -8.25 to -1.55), but not 52 weeks (1 RCT, n = 105, MD -4.80, 95% CI -9.79 to 0.19). Similar numbers of participants from each group left the study

	early (1 RCT, n = 106, RR 1.27, 95% CI 0.72 to 2.22, *very low quality evidence*). *Fazit: no overall difference in the effectiveness of the two treatment combinations; however, the aripiprazole combination caused fewer side effects.* **Clozapine plus amisulpride versus clozapine plus quetiapine** One study showed a significant benefit of amisulpride over quetiapine in the short term, for both change in global state (Clinical Global Impression (CGI): 1 RCT, n = 50, MD -0.90, 95% CI -1.38 to -0.42, *very low quality evidence*) and mental state (Brief Psychiatric Rating Scale (BPRS): 1 RCT, n = 50, MD -4.00, 95% CI -5.86 to -2.14, *low quality evidence*). Similar numbers of participants from each group left the study early (1 RCT, n = 56, RR 0.20, 95% CI 0.02 to 1.60, *very low quality evidence*) *Fazit: the amisulpride combination was more effective in treating schizophrenia in comparison with the quetiapine combination.* **Clozapine plus risperidone versus clozapine plus sulpiride** There was no difference between risperidone and sulpiride for clinically significant response, defined by the study as 20% to 50% reduction in Positive and Negative Syndrome Scale (PANSS) (1 RCT, n = 60, RR 0.82, 95% CI 0.40 to 1.68, very low quality evidence). There were similar equivocal results for weight gain (1 RCT, n = 60, RR 0.40, 95% CI 0.08 to 1.90, very low quality evidence) and mental state (PANSS total: 1 RCT, n = 60, MD -2.28, 95% CI -7.41 to 2.85, very low quality evidence). No-one left the study early. *Fazit: there were no overall differences in clinical effectiveness between these combinations.* **Clozapine plus risperidone versus clozapine plus ziprasidone** There was no difference between risperidone and ziprasidone for clinically significant response (1 RCT, n = 24, RR 0.80, 95% CI 0.28 to 2.27, *very low quality evidence*), change in global state CGI-II score (1 RCT, n = 22, MD -0.30, 95% CI -0.82 to 0.22, *very low quality evidence*), change in PANSS total score (1 RCT, n = 16, MD 1.00, 95% CI -7.91 to 9.91, *very low quality evidence*) or leaving the study early (1 RCT, n = 24, RR 1.60, 95% CI 0.73 to 3.49, *very low quality evidence*). *Fazit: neither combination showed superiority over the other in improving the symptoms of schizophrenia* **Clozapine plus ziprasidone versus clozapine plus quetiapine** One study found, in the medium term, a superior effect for ziprasidone combination compared with quetiapine combination for clinically significant response in mental state (> 50% reduction PANSS: 1 RCT, n = 63, RR 0.54, 95% CI 0.35 to 0.81, *low quality evidence*), global state (CGI - Severity score: 1 RCT, n = 60, MD -0.70, 95% CI -1.18 to -0.22, *low quality evidence*) and mental state (PANSS total score: 1 RCT, n = 60, MD -12.30, 95% CI -22.43 to -2.17, *low quality evidence*). There was no effect for leaving the study early (1 RCT, n = 63, RR 0.52, CI 0.05 to 5.41, *very low quality evidence*). *Fazit: the ziprasidone combination was more effective in improving both mental and global state than the quetiapine combination.*
	4. Anmerkungen/Fazit der Autoren The reliability of results from this review is limited, evidence is of low or very low quality. Furthermore, due to the limited number of included studies, we were unable to undertake formal meta-analyses. As a consequence, any

	conclusions drawn from these findings are based on single, small-sized RCTs with high risk of type II error. Properly conducted and adequately powered RCTs are required. Future trialists should seek to measure patient-important outcomes such as quality of life, as well as clinical response and adverse effects. 5. *(Im Einzelfall: Kommentar zu Review)* - *heterogenes Studienkollektiv* - *low quality der eingeschlossenen Studien* - *Poolen der Studienergebnisse nicht möglich (Studien-Heterogenität)*
Sampson S et al., 2016 [25]. Risperidone (depot) for schizophrenia (Review)	1. Fragestellung To examine the effects of depot risperidone for treatment of schizophrenia or related psychoses in comparison with placebo, no treatment or other antipsychotic medication • original published version of this review (Hosalli 2003) • updates in 2010, 2012 and 2015 identified 181 references *with no additional records identified through other sources*
	2. Methodik Population: People with schizophrenia and schizophrenia-like disorders such as schizophreniform disorder, delusional disorder or schizoaffective disorder, diagnosed by any criteria. Intervention: Risperidone (long-acting intramuscular injection, any dose) Komparator: Placebo or no treatment; Other antipsychotic drugs (depot) Any dose, administered in depot form; Other antipsychotic drugs (oral) Endpunkt: Primäre Endpunkte: Global state, Mental state; Sekundäre Endpunkte: u.a. Death - suicide and natural causes, Global state, QoL, Adverse Effects Suchzeitraum (Aktualität der Recherche): Oktober 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 RCTs (N=5723) Qualitätsbewertung der Studien: Cochrane Handbook for Systematic Reviews of Interventions
	3. Ergebnisdarstellung <u>Eingeschlossene Studien:</u> - Only one study compared depot risperidone with placebo (Kane 2002*). - Of the studies comparing depot risperidone with another single antipsychotic: o two used oral risperidone at 2 mg to 6 mg per day (Bai 2006; Chue 2002); o one study investigated 5mg to 20mg/day oral olanzapine (Keks 2007), o and one compared depot risperidone against 5 mg to 30 mg/day oral aripiprazole (MacFadden 2010). - Covell 2012 compared either haloperidol decanoate or fluphenazine (no doses prescribed, but used at 'clinician's judgement'; - Gaebel 2010* was mainly concerned with quetiapine at up to 750 mg/day, but also featured a smaller aripiprazole armof 10mg to 30mg per

	day. - The remaining three studies randomised patients to receive depot risperidone or to remain on their current oral antipsychotic: o in the case of Quinn 2012*, only second-generation “atypical” drugs were used, specifically risperidone, olanzapine and quetiapine; o Rosenheck 2011provides no details of which drugs were used. *Hinweis: Placebovergleiche werden nicht berichtet* Qualitätsbewertung: The quality of evidence presented is, in the main, low and at best moderate. Depot injections are often used on people who refuse treatment. Such people are difficult to include in studies. **Risperidone depot versus general oral antipsychotics** The outcome of improvement in mental state was not presented due to high levels of attrition, nor were levels of severe adverse events explicitly reported. Most primary outcomes of interest showed no difference between treatment groups. However,more people receiving depot risperidone experienced nervous system disorders (long-term:1 RCT, n=369, RR 1.34 95% CI 1.13 to 1.58, *very-low quality evidence*). **Risperidone depot versus oral risperidone (Bai 2006; Chue 2002, n = 690)** Data for relapse and severe adverse events were not reported. All outcomes of interest were rated as *moderate quality evidence*. Main results showed no differences between treatment groups with equivocal data for change in mental state, numbers leaving the study early, any extrapyramidal symptoms, weight increase and prolactin-related adverse events. **Risperidone depot versus oral quetiapine (n = 666, Gaebel 2010)** Relapse rates and improvement in mental state were not reported. Fewer people receiving risperidone depot left the study early (longterm: 1 RCT, n=666, RR 0.84 95%CI 0.74 to 0.95, *moderate quality evidence*). Experience of serious adverse events was similar between groups (*low quality evidence*), but more people receiving depot risperidone experienced EPS (1 RCT, n=666, RR 1.83 95% CI 1.07 to 3.15, *low quality evidence*), had greater weight gain (1 RCT, n=666, RR 1.25 95% CI 0.25 to 2.25, *low quality evidence*) and more prolactin-related adverse events (1 RCT, n=666, RR 3.07 95% CI 1.13 to 8.36*, very low quality evidence*). **Risperidone depot versus oral aripiprazole (n = 730, Gaebel 2010; MacFadden 2010)** Relapse rates, mental state using PANSS, leaving the study early, serious adverse events and weight increase were similar between groups. However more people receiving depot risperidone experienced prolactin-related adverse events compared to those receiving oral aripiprazole (2 RCTs, n=729, RR 9.91 95% CI 2.78 to 35.29, *very low quality of evidence*). **Risperidone depot versus oral olanzapine (The only study comparing risperidone depot to oral olanzapine (Keks 2007) did not include relapse as an outcome)** Relapse rates were not reported in any of the included studies for this comparison. Improvement in mental state using PANSS and instances of severe adverse events were similar between groups. More people receiving depot risperidone left the study early than those receiving oral olanzapine (1 RCT, n=618, RR 1.32 95% CI 1.10 to 1.58, *low*

	quality evidence) with those receiving risperidone depot also experiencing more extrapyramidal symptoms (1 RCT, n=547, RR 1.67 95% CI 1.19 to 2.36, *low quality evidence*). However, more people receiving oral olanzapine experienced weight increase (1 RCT, n=547, RR 0.56 95% CI 0.42 to 0.75, *low quality evidence*). **Risperidone depot versus atypical depot antipsychotics (specifically paliperidone palmitate) (Fleischhacker 2011; Li 2011; Pandina 2011)** Relapse rates were not reported and rates of response using PANSS, weight increase, prolactin-related adverse events and glucose-related adverse events were similar between groups. Fewer people left the study early due to lack of efficacy from the risperidone depot group (long term: 1 RCT, n=749, RR 0.60 95% CI 0.45 to 0.81, *low quality evidence*), but more people receiving depot risperidone required use of EPS-medication (2 RCTs, n=1666, RR 1.46 95% CI 1.18 to 1.8, *moderate quality evidence*). **Risperidone depot versus typical depot antipsychotics (Covell 2012, n = 62)** Outcomes of relapse, severe adverse events or movement disorders were not reported. Outcomes relating to improvement in mental state demonstrated no difference between groups (*low quality evidence*). However, more people receiving depot risperidone compared to other typical depots left the study early (long-term:1 RCT, n=62, RR 3.05 95% CI 1.12 to 8.31, *low quality evidence*).
	4. Anmerkungen/Fazit der Autoren It is difficult to know from the results of this review if depot risperidone is any more effective in treating the symptoms of schizophrenia than placebo or other treatments. For people who are happy to take oralmedication, depot risperidone is about equal to oral risperidone. People on oral risperidone may continue to benefit if treated with depot risperidone, without the need to take tablets. However, in high doses, depot risperidone can have serious side effects, particularly movement disorders, uncontrollable shaking, spasms and tremors. Depot risperidone may bring this new antipsychotic to people who stop taking their tablets, so helping reduce relapse and with little increased risk of side effects.
Sampford JR et al., 2016 [24]. Fluphenazine (oral) versus atypical antipsychotics for schizophrenia (Review)	1. Fragestellung To measure the outcomes (both beneficial and harmful) of the clinical effectiveness, safety and cost-effectiveness of oral fluphenazine versus atypical antipsychotics for schizophrenia.
	2. Methodik Population: Adults (aged 18 and over) with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, again by any means of diagnosis. Intervention: Oral fluphenazine Komparator: Atypical oral antipsychotics, Endpunkt: Primäre Endpunkte: Clinically important response; Sekundäre Endpunkte: u.a. Death, QoL, AEs Suchzeitraum (Aktualität der Recherche): April 2013

	Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 RCTs (N=202) Qualitätsbewertung der Studien: Cochrane Handbook for Systematic Reviews of Interventions
	3. Ergebnisdarstellung <u>Eingeschlossenen Studien:</u> - Amisulpride vs. Fluphenazine (2 Studien) - Olanzapine vs. Fluphenazine (1 Studie) - Quetiapine vs. Fluphenazine (1 Studie) - Risperidone vs. Fluphenazine (1 Studie) <u>Qualitätsbewertung:</u> Evidence from these few trials is poor, of low quality and involves a small number of participants. Hinweis: It was not possible to perform an overall analysis because the four studies were too different. Therefore, all results were based on data from one study per comparison. **fluphenazine with amisulpride (2 Studien)** Comparing oral fluphenazine with amisulpride, there was no difference between groups for mental state using the Brief Psychiatric Rating Scale (BPRS) (1 RCT, n = 57, MD 5.10 95% CI -2.35 to 12.55, *very low-quality evidence*), nor was there any difference in numbers leaving the study early for any reason (2 RCTs, n = 98, RR 1.19 95% CI 0.63 to 2.28, *very low-quality evidence*).More people required concomitant anticholinergic medication in the fluphenazine group compared to amisulpride (1 RCT, n = 36, RR 7.82 95% CI 1.07 to 57.26, *very low-quality evidence*). No data were reported for important outcomes including relapse, changes in life skills, quality of life or cost-effectiveness. **fluphenazine with risperidone (1 Studien)** Comparing oral fluphenazine with risperidone, data showed no difference between groups for 'clinically important response' (1 RCT, n = 26, RR 0.67 95% CI 0.13 to 3.35, *very low-quality evidence*) nor leaving the study early due to inefficacy (1 RCT, n = 25, RR 1.08 95% CI 0.08 to 15.46, *very low-quality evidence*). No data were reported data for relapse; change in life skills; quality of life; extrapyramidal adverse effects; or cost-effectiveness. **Quetiapine vs. Fluphenazine (1 Studie)** Once again there was no difference when oral fluphenazine was compared with quetiapine for clinically important response (1 RCT, n = 25, RR 0.62 95% CI 0.12 to 3.07, *very low-quality evidence*), nor leaving the study early for any reason (1 RCT, n = 25, RR 0.46 95% CI 0.05 to 4.46, *very low-quality evidence*). No data were reported for relapse; clinically important change in life skills; quality of life; extrapyramidal adverse effects; or cost-effectiveness. **Olanzapine vs. Fluphenazine (1 Studie)** Compared to olanzapine, fluphenazine showed no superiority for clinically important response (1 RCT, n = 60, RR 1.33 95% CI 0.86 to 2.07, *very low-quality evidence*), in incidence of akathisia (1 RCT, n = 60, RR 3.00 95% CI 0.90 to 10.01, *very low-quality evidence*) or in people leaving the study early (1 RCT, n = 60, RR 3.00 95% CI 0.33 to 27.23, *very low-quality evidence*). No data were reported for relapse; change in life skills; quality of life; or cost-effectiveness.
	4. Anmerkungen/Fazit der Autoren

	Measures of clinical response andmental state do not highlight differences between fluphenazine and amisulpride, risperidone, quetiapine or olanzapine. Largely measures of adverse effects are also unconvincing for substantive differences between fluphenazine and the newer drugs. All included trials carry a substantial risk of bias regarding reporting of adverse effects and this bias would have favoured the newer drugs. The four small short included studies do not provide much clear information about the relative merits or disadvantages of oral fluphenazine compared with newer atypical antipsychotics. Fluphenazine is low cost and widely available, so is likely to remain one of themost widely used treatments for schizophrenia worldwide. However, evidence currently available from randomised controlled trials about its effectiveness compared to atypical antipsychotics is unclear. 5. *(Im Einzelfall: Kommentar zu Review /LL)* - *low quality der eingeschlossenen Studien* - *Poolen der Studienergebnisse nicht möglich (Studien-Heterogenität)*
Naeem F et al., 2015 [17]. Cognitive behavioural therapy (brief versus standard duration) for schizophrenia (Review)	1. Fragestellung To review the effects of brief CBTp (6 to 10 regular sessions given in less than 4 months and using a manual) for people with schizophrenia compared with standard CBTp (12 to 20 regular sessions given in 4 to 6 months and using a manual).
	2. Methodik Population: Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, by any means of diagnosis. Intervention: brief cognitive behavioural therapy (CBTp) Komparator: standard CBTp Endpunkt: Primäre Endpunkte: u.a. Global state (Clinically-important response), QoL; Sekundäre Endpunkte: u.a. Death, AEs Suchzeitraum (Aktualität der Recherche): August 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): no included studies in this review. Qualitätsbewertung der Studien: Cochrane Handbook for Systematic Reviews of Interventions
	3. Ergebnisdarstellung We found only seven studies which used a brief version of CBTp, but no study compared brief CBTp with CBTp of standard duration. No studies could be included.
	4. Anmerkungen/Fazit der Autoren Currently there is no literature available to compare brief with standard CBTp for people with schizophrenia. We cannot, therefore, conclude whether brief CBTp is as effective, less effective or even more effective than standard courses of the same therapy. This lack of evidence for brief CBTp has serious implications for research and practice.Well planned, conducted and reported randomised trials are indicated.

Maayan N et al., 2015 [15]. Fluphenazine decanoate (depot) and enanthate for schizophrenia (Review)	1. Fragestellung To assess the effects of fluphenazine decanoate and enanthate versus oral anti-psychotics and other depot neuroleptic preparations for individuals with schizophrenia in terms of clinical, social and economic outcomes. - *Update Oktobrt 2013* - *Original Februar 2011*
	2. Methodik Population: people with schizophrenia Intervention: fluphenazine decanoate or enanthate Komparator: placebo or oral anti-psychotics or other depot preparations Endpunkt: Primäre Endpunkte: u.a. Death and all causes of mortality, Clinical global state (Relapse, Clinically significant change in global state - as defined by each of the studies; Sekundäre Endpunkte: u.a Clinical global state (Mean score/change in global state), Behaviour, QoL, AEs Suchzeitraum (Aktualität der Recherche): Anzahl eingeschlossene Studien/Patienten (Gesamt):73 RCTs (N=4870) Qualitätsbewertung der Studien: Cochrane Handbook for Systematic Reviews of Interventions
	3. Ergebnisdarstellung <u>Eingeschlossenen Studien:</u> - Ten studies compared *fluphenazine decanoate with enanthate* (Altamura 1985; Asarnow 1988; Chouinard 1978; Chouinard 1982; Donlon 1976; Kane 1978; Keskiner 1971; Kurland 1966; MacCrimmon 1978; Van Praag 1973). - Fourteen studies compared *fluphenazine esters with oral antipsychotics*. - Thirty-five trials compared *fluphenazine decanoate or enanthate with other depot formulations*. - There were 10 dosage studies - nine comparing fluphenazine decanoate and one comparing fluphenazine enanthate (Goldstein 1978). - Of the 73 included trials, 66 used fluphenazine decanoate as an intervention. *Hinweis: Placebovergleiche werden nicht berichtet* <u>Qualitätsbewertung:</u> the quality of the evidence is low to very low **Fluphenazine decanoate versus oral neuroleptics** Death und Hospital admission: No studies reported data for this outcome low quality evidence from six studies showed that medium term rates of relapse were not significantly different in the fluphenazine decanoate group (49%) compared with oral neuroleptics (42%). Low-quality evidence showed no difference in the number of participants leaving the study early for fluphenazine decanoate (17%) versus oral neuroleptics (18%). Very low quality evidence from one study (Simon 1978) found no difference in mental state measured on the BPRS. Three small studies showed that general extrapyramidal adverse effects were lower in the fluphenazine decanoate group (7%) compared to oral

	neuroleptics (14%). However, the quality of the evidence was judged to be very low, and there was no difference with longer-term data. **Fluphenazine decanoate versus other depot antipsychotics** One study did report a death in fluphenazine decanoate treatment group, however, this did produce an effect with no significant differences between groups for death. Eleven studies reported equivocal data fro the outcome of 'relapse' at six months to one year.Other global state outcomes such as significant clinical improvement, clinical global impression, needing additional antipsychotics and 'not improved' were also equivocal. Fifteen included trials found people were no more likely to leave the study early if they were receiving fluphenazine decanoate or other depot antipsychotics. Only one study reported equivocal data on Behaviour. Short- and medium-term studies assessing mental state (BPRS endpoint scores) to significantly favour 'other depot neuroleptics' for the short term and medium term. Long-term studies did not find such difference in mental state. One study reported on the outcome of depression; Dencker 1973, found no significant difference between fluphenazine decanoate and pipothiazine palmitate. General adverse effects (short-termdata) were reported by Frangos 1978 and Javed 1991 and favoured other depot neuroleptics. However, medium-term data were equivocal. **Fluphenazine decanoate versus fluphenazine enanthate** Death/ Clinically significant change in global state/ Hospital admission: No studies reported data for this outcome. Very low quality evidence from only one small study (MacCrimmon 1978) found no significant difference in the number of participants experiencing relapse in the medium term. Results were also equivocal for immediate- and short-term studies. No difference in the number of participants leaving the study early was found between fluphenazine decanoate (29%) and fluphenazine enanthate (12%), but this is based on one small study (MacCrimmon 1978) and considered to be very low quality evidence. BPRS data were only available fromone small trial (MacCrimmon 1978). This study reported identical scores for both of the fluphenazine depots groups. Very low evidence from two very small studies showed that two preparations caused roughly equal incidences of generalmovement disorders. Results were also equivocal for parkinsonism, akathisia and needing additional anticholinergics in the short and immediate term.
	4. Anmerkungen/Fazit der Autoren There aremore data for fluphenazine decanoate than for the enanthate ester. Both are effective antipsychotic preparations. Fluphenazine decanoate produced fewer movement disorder effects than other oral antipsychotics but data were of low quality, and overall, adverse effect data were equivocal. In the context of trials, there is little advantage of these depots over oral medications in terms of compliance but this is unlikely to be applicable to everyday clinical practice.
Hartung B et al., 2015 [9]. Perphenazine for	1. Fragestellung To examine the clinical effects and safety of perphenazine for those with schizophrenia and schizophrenia-like psychoses.

schizophrenia (Review)	*Update 2013*
	2. Methodik Population: People with schizophrenia and schizophrenia-like disorders such as schizophreniform disorder, delusional disorder or schizoaffective disorder, diagnosed by any criteria. Intervention: Perphenazine Komparator: Placebo or no treatment, Other antipsychotic drugs Endpunkt: Primäre Endpunkte: Clinical response (Global or mental state); Sekundäre Endpunkte: u.a. AEs, Behaviour, QoL Suchzeitraum (Aktualität der Recherche): September 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt):31 RCTs (N=4522) Qualitätsbewertung der Studien: GRADE (Grading of Recommendations Assessment, Development and Evaluationtool) and assessed risk of bias
	3. Ergebnisdarstellung <u>Eingeschlossene Studien:</u>

Control Intervention	Average dose (control)	Studies	Average dose (perphenazine)
vs Placebo	to match study drug	Chouinard 1975; Chouinard 1977; Collins 1967; Hanlon 1964	mean 13 mg/day
vs Aripiprazole	mean 26.8 mg/day	Kane 2003; Zhang 2010	mean 25.15 mg/day
vs Benperidol	range 6 or 12 mg/day	Eckmann 1984	range 12 or 24 mg/day
vs Bromperidol	mean 6 mg/day	Woggon 1978	mean 20 mg/day
vs Chlorpromazine	mean 487.63 mg/day	Bennett 1961; Hanlon 1965; Kurland 1961	mean 40.91 mg/day
vs Clocapramine	range 75 to 150 mg/day	Kurihara 1983	range 9 to 18 mg/day
vs Clopenthixol	range 25 to 250 mg/day	Dehnel 1968	range 8 to 80 mg/day
vs Clothiapine	range 12 mg/day increased to 24 mg/day	Itoh 1969	range 45 mg/day increased to 90 mg/day
vs Clozapine	range 0 to 600 mg/day	Sun 2000; Van Praag 1976	range 0 to 60 mg/day
vs Clozapine + perphenazine	range 32 to 50 mg + 100 to 300 mg/mg/day	Sun 2000	range 8 to 60 mg/day
vs Fluphenazine	mean 5.92 mg/day	Hanlon 1965	mean 38.61 mg/day
vs Haloperdiol	range 3 to 6 mg/day	Kurihara 1983	range 9 to 18 mg/day
vs Loxapine	range 20 mg/day to max 150 mg/day	Fruensgaard 1978	range 16 mg/day to max 120 mg/day
vs Mepazine	mean 151 mg/day	Bennett 1961; Kurland 1961	mean 42 mg/day
vs Methyperidol	range 15 mg to 30 mg/day	Itoh 1969 III	range 9 mg/day to 18 mg/day
vs Olanzapine	mean 16.5 mg/day	CATIE 2005; Naukkarinen 2000; Wang 2008b	mean 24.9 mg/day
vs Penfluridol	2 mg/day the flexible up to max 100 mg/day	Itoh 1976	12 mg/day then flexible dose age up to max 60 mg/day
vs Prochlorperazine	mean 59.9 mg/day	Bennett 1961; Hanlon 1965; Kurland 1961	mean 40.91 mg/day
vs Quetiapine	mean 401.16 mg/day	CATIE 2005; Wang 2008c	mean 22.65 mg/day

vs Promazine	mean 438.92 mg/day	Kurland 1961	mean 30.83 mg/day
vs Risperidone	mean 5.3 mg/day	CATIE 2005; Hoyberg 1993; Wang 2008a	mean 25.4 mg/day
vs Sulpiride	mean 900 mg/day	Amakusa 1973; Lepola 1989	mean 20.5 mg/day
vs Thioproprazate	mean 20.83 mg/day	Hanlon 1965	mean 38.61 mg/day
vs Thioridazine	mean 193.46 mg/day	Hanlon 1965	mean 38.61 mg/day
vs Thiothixene	no details	Itoh 1969 II	no details
vs Timiperone	range 2 mg/day up to max of 12 mg/day	Takahashi 1982	range 8 mg/day up to max of 48 mg/day
vs Trifluoperazine	mean 11.49 mg/day	Hanlon 1965	mean 38.61 mg/day
vs Trifluopromazine	mean 124.13 mg/day	Bennett 1961; Hanlon 1965; Kurland 1961	mean 40.9 mg/day
vs Ziprasidone	mean 112.8 mg/day	CATIE 2005	mean 20.8 mg/day
vs Zotepine	range 75 mg/day to max 150 mg/day	Imai 1980	range 12 mg/day to max 24 mg/day
vs Zuclopenthixol	mean 37 mg/day	Remvig 1987	mean 30 mg/day

Qualitätsbewertung: The quality of evidence presented by the trials was rated by the review authors to be very low quality.

Hinweis: Placebovergleiche werden nicht berichtet

For the comparison of perphenazine versus any other antipsychotic drugs, no real differences in effect between the drugs were found.

no significant difference between groups for those considered 'no better or deterioration' (17 RCTs, n = 1879, RR 1.04 CI 0.91 to 1.17, very low quality evidence).

For mental state outcome of 'no effect' of the study drug, there was again no significant difference between groups (4 RCTs, n = 383, RR 1.24 CI 0.61 to 2.52, very low quality evidence). Death was not reported in any of the included studies.

no significant difference in rates of dystonia with perphenazine versus any other antipsychotic drugs (4 RCTs, n = 416, RR 1.36 CI 0.23 to 8.16, very low quality evidence), nor was there a significant difference between groups for serious adverse events (2 RCTs, n = 1760, RR 0.98 CI 0.68 to 1.41, very low quality evidence).

4. Anmerkungen/Fazit der Autoren

Although perphenazine has been used in randomised trials for more than 50 years, incomplete reporting and the variety of comparators usedmake it impossible to draw clear conclusions. All data for themain outcomes in this review were of very low quality evidence. At best we can say that perphenazine showed similar effects and adverse events as several of the other antipsychotic drugs. Since perphenazine is a relatively inexpensive and frequently used compound, further trials are justified to clarify the properties of this classical antipsychotic drug.

Buckley LA et al., 2015 [3].

Supportive therapy for schizophrenia

1. Fragestellung

To review the effects of supportive therapy compared with standard care, or other treatments in addition to standard care for people with schizophrenia.

Update: Nov. 2012

(Review)	2. Methodik Population: people with schizophrenia or schizophrenia-like illnesses using any criteria. Intervention: supportive therapy *Definition: These interventions are provided by a single person with the main purpose of maintaining current functioning or assisting pre-existing coping abilities in people who have a diagnosis of schizophrenia or schizophrenia-like illness. The therapies can be aimed at individuals or groups of people.* Komparator: any other treatment or standard care. Endpunkt: Primäre Endpunkte: Global state (Relapse), Service outcomes (Hospitalisation), General functioning (No clinically important change in general functioning), Sekundäre Endpunkte: u.a. QoL, Death, Behaviour Suchzeitraum (Aktualität der Recherche): Nov. 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 24 RCTs (N=2126) Qualitätsbewertung der Studien: Cochrane Handbook for Systematic Reviews of Interventions
	3. Ergebnisdarstellung <u>Eingeschlossene Studien:</u> All studies used supportive therapy in addition to standard care (including antipsychotic medication). Five studies compared supportive therapywith standard treatment alone (Coyle 1988; Davidson 2004; Durham 2003; Lewis 2002b; Tarrier 1998), the remaining trials used various other psychosocial interventions for comparison. Twelve studies compared supportive therapy with CBT (Durham 2003; Haddock 1999; Hogarty 1997-study 1; Hogarty 1997-study 2; Kemp 1996; Levine 1998; Lewis 2002b; Pinto 1999; Sensky 2000b; Spaulding 1999; Tarrier 1998; Turkington 2000). Two studies used family therapy as a comparison (Falloon 1982; Hogarty 1997-study 1). Skills training was investigated in three studies (Coyle 1988; Eckman 1992; Wirshing 1991); other comparisons were personal therapy plus family therapy (Hogarty 1997-study 1), psychoeducation (Coyle 1988; Uzenoff 2007), milieu rehabilitation programme (Dincin 1982) and insight-oriented psychotherapy (Stanton 1984). One study investigated supportive therapy combined with client-focused case management in comparison with client-focused case management (O'Donnell 1999). One trial compared supportive therapy with intensive case management in comparison with intensive case management (Klein 1998). Finally, one trial investigated the effect of adding supportive therapy to a combination of social skills training andmedication (Malm 1982). Fourteen of the studies attempted to match experimental and control psychosocial interventions for the amount of therapist contact (Eckman 1992; Falloon 1982; Haddock 1999; Kemp 1996; Levine 1998; Lewis 2002b; Penn 2009; Pinto 1999; Sensky 2000b; Spaulding 1999;Tarrier 1998; Turkington 2000; Uzenoff 2007; Wirshing 1991). In contrast, four studies took the approach that different interventions by their nature involve different amounts of therapist contact (Dincin 1982; Hogarty 1997-study 1; Hogarty 1997-study 2; Stanton 1984). The other studies did not report on this matter. Davidson 2004 gave all participants a $28 stipend whether they received supportive care or not to control for possible effects of receiving funds to take part in social activities. <u>Qualitätsbewertung:</u> Overall, the evidence was very low quality. no significant differences in the primary outcomes of relapse, hospitalisation and general functioning between supportive therapy and standard care. significant differences favouring other psychological or psychosocial

	treatments over supportive therapy. These included hospitalisation rates (4 RCTs, n = 306, RR 1.82 CI 1.11 to 2.99, very low quality of evidence), clinical improvement in mental state (3 RCTs, n = 194, RR 1.27 CI 1.04 to 1.54, very low quality of evidence) and satisfaction of treatment for the recipient of care (1 Supportive therapy RCT, n = 45, RR 3.19 CI 1.01 to 10.7, very low quality of evidence). For this comparison, we found no evidence of significant differences for rate of relapse, leaving the study early and quality of life. When we compared supportive therapy to cognitive behavioural therapy CBT), we again found no significant differences in primary outcomes. There were very limited data to compare supportive therapy with family therapy and psychoeducation, and no studies provided data regarding clinically important change in general functioning, one of our primary outcomes of interest.
	4. Anmerkungen/Fazit der Autoren There are insufficient data to identify a difference in outcome between supportive therapy and standard care. There are several outcomes, including hospitalisation and general mental state, indicating advantages for other psychological therapies over supportive therapy but these findings are based on a few small studies where we graded the evidence as very low quality. Future research would benefit from larger trials that use supportive therapy as the main treatment arm rather than the comparator.
Mahapatra J et al., 2014 [16]. Flupenthixol decanoate (depot) for schizophrenia or other similar psychotic disorders (Review)	1. Fragestellung To evaluate the effects of flupenthixol decanoate in comparison with placebo, oral antipsychotics and other depot neuroleptic preparations for people with schizophrenia and other severe mental illnesses, in terms of clinical, social and economic outcomes. Update: April 2013
	2. Methodik Population: Peoplewith schizophrenia or other similar psychotic disorders (e.g. schizophreniform, schizoaffective disorders), irrespective of diagnostic criteria used, were included. Intervention: flupenthixol decanoate Komparator: placebo or other antipsychotic drugs Endpunkt: Primäre Endpunkte: Clinical response (Relapse, Clinically significant response in global state - as defined by each of the studies), Service utilisation outcomes (Hospital admission); Sekundäre Endpunkte: u.a. QoL, AEs, Behaviour Suchzeitraum (Aktualität der Recherche): April 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 15 RCTs (N=626) Qualitätsbewertung der Studien: Cochrane Handbook for Systematic Reviews of Interventions
	3. Ergebnisdarstellung <u>Eingeschlossene Studien:</u> - No trial compared the depot formulation with placebo. - Only one study compared flupenthixol decanoate with an oral antipsychotic, penfluridol (Gerlach 1975). - Four studies compared different dosages of flupenthixol decanoate (Cookson 1983; Cookson 1987; Johnson 1987; McCreadie 1979).

	- Ten studies compared depot flupenthixol with other depots haloperidol decanoate (Eberhard 1986), fluphenazine decanoate (Javed 1991;Kelly1977; Lundin 1990; Pinto 1979;Wistedt 1982; Wistedt 1983), clopenthixol decanoate (Martyns 1993), pipotiazine palmitate (Steinert 1986), and perphenazine enanthate (Eufe 1979). Qualitätsbewertung: data reported are of low or very low quality and this review One small study compared flupenthixol decanoate with an oral antipsychotic (penfluridol). Only two outcomes were reported with this single study, and it demonstrated no clear differences between the two preparations as regards leaving the study early (n = 60, 1 RCT, RR 3.00, CI 0.33 to 27.23, *very low quality evidence*) and requiring anticholinergic medication (1 RCT, n = 60, RR 1.19, CI 0.77 to 1.83, *very low quality evidence*). Ten studies in total compared flupenthixol decanoate with other depot preparations, though not all studies reported on all outcomes of interest. There were no significant differences between depots for outcomes such as relapse at medium term (n = 221, 5 RCTs, RR 1.30, CI 0.87 to 1.93, *low quality evidence*), and no clinical improvement at short term (n = 36, 1 RCT, RR 0.67, CI 0.36 to 1.23, *low quality evidence*). There was no difference in numbers of participants leaving the study early at short/medium term (n = 161, 4 RCTs, RR 1.23, CI 0.76 to 1.99, *low quality evidence*) nor with numbers of people requiring anticholinergic medication at short/medium term (n = 102, 3 RCTs, RR 1.38, CI 0.75 to 2.25, *low quality evidence*). Three studies in total compared high doses (100 to 200 mg) of flupenthixol decanoate with the standard doses (~40mg) per injection. Two trials found relapse at medium term (n = 18, 1 RCT, RR 1.00, CI 0.27 to 3.69, *low quality evidence*) to be similar between the groups. However people receiving a high dose had slightly more favourable medium term mental state results on the Brief Psychiatric Rating Scale (BPRS) (n = 18, 1 RCT, MD -10.44, CI -18.70 to -2.18, *low quality evidence*). There was also no significant difference in the use of anticholinergic medications to deal with side effects at short term (2 RCTs n = 47, RR 1.12, CI 0.83 to 1.52 *very low quality evidence*). One trial comparing a very low dose of flupenthixol decanoate (~6 mg) with a low dose (~9 mg) per injection reported no difference in relapse rates (n = 59, 1 RCT, RR 0.34, CI 0.10 to 1.15, *low quality evidence*).
	4. Anmerkungen/Fazit der Autoren In the current state of evidence, there is nothing to choose between flupenthixol decanoate and other depot antipsychotics. From the data reported in clinical trials, it would be understandable to offer standard dose rather than the high dose depot flupenthixol as there is no difference in relapse. However, data reported are of low or very low quality and this review highlights the need for large, welldesigned and reported randomised clinical trials to address the effects of flupenthixol decanoate.
Khanna P et al., 2014 [13]. Aripiprazole versus other atypical antipsychotics for schizophrenia (Review)	1. Fragestellung To review the effects of aripiprazole compared with other atypical antipsychotics for people with schizophrenia and schizophrenia-like psychoses. This review was published in early 2013 with a vast number of Chinese studies in awaiting classification, thus we have updated it again in June 2013
	2. Methodik Population: people with schizophrenia or schizophrenia-like psychoses

	Intervention: aripiprazole (oral) Komparator: oral and parenteral forms of amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone or zotepine Endpunkt: Primäre Endpunkte: Global state (No clinically important response), AEs, General functioning; Sekundäre Endpunkte: u.a. Global State, QoL Suchzeitraum (Aktualität der Recherche): Anzahl eingeschlossene Studien/Patienten (Gesamt): 174 Studien (N=17,244) Qualitätsbewertung der Studien: Cochrane Handbook for Systematic Reviews of Interventions
	3. Ergebnisdarstellung Eingeschlossene Studien: Other atypical drugs, namely olanzapine, risperidone, ziprasidone and quetiapine were used as controls. As some studies did not elucidate doses it can only be presumed that therapeutic doses were employed. Qualitätsbewertung: quality of the evidence is all low or very low **aripiprazole (oral) vs. clozapine** When compared with clozapine, there were no significant differences for global state (no clinically significant response, n = 2132, 29 RCTs, *low quality evidence*); mental state (BPRS, n = 426, 5 RCTs, *very low quality evidence*); or leaving the study early for any reason (n = 240, 3 RCTs, *very low quality evidence*). Quality of life score using theWHO-QOL-100 scale demonstrated significant difference, favouring aripiprazole (n = 132, 2 RCTs, RR 2.59 CI 1.43 to 3.74, *very low quality evidence*). General extrapyramidal symptoms (EPS) were no different between groups (n = 520, 8 RCTs,*very low quality evidence*). No study reported general functioning or service use. **aripiprazole (oral) vs. quetiapine** When compared with quetiapine, there were no significant differences for global state (n = 991, 12 RCTs, *low quality evidence*); mental state (PANSS positive symptoms, n = 583, 7 RCTs, *very low quality evidence*); leaving the study early for any reason (n = 168, 2 RCTs, *very low quality evidence*), or general EPS symptoms (n = 348, 4 RCTs, *very low quality evidence*). Results were significantly in favour of aripiprazole for quality of life (WHO-QOL-100 total score, n = 100, 1 RCT, MD 2.60 CI 1.31 to 3.89, *very low quality evidence*). No study reported general functioning or service use. **aripiprazole (oral) vs. risperidone** When compared with risperidone, there were no significant differences for global state (n = 6381, 80 RCTs, *low quality evidence*); or leaving the study early for any reason (n = 1239, 12 RCTs, *very low quality evidence*). Data were significantly in favour of aripiprazole for improvement in mental state using the BPRS (n = 570, 5 RCTs, MD 1.33 CI 2.24 to 0.42, *very low quality evidence*); with higher adverse effects seen in participants receiving risperidone of general EPS symptoms (n = 2605, 31 RCTs, RR 0.39 CI 0.31 to 0.50, *low quality evidence*). No study reported general functioning, quality of life or service use. **aripiprazole (oral) vs. ziprasidone** When compared with ziprasidone, there were no significant differences for global state (n = 442, 6 RCTs, *very low quality evidence*); mental state using the BPRS (n = 247, 1 RCT, *very low quality evidence*); or leaving the study

	early for any reason (n = 316, 2 RCTs, *very low quality evidence*). Weight gain was significantly greater in people receiving aripiprazole (n = 232, 3 RCTs, RR 4.01 CI 1.10 to 14.60, *very low quality evidence*). No study reported general functioning, quality of life or service use. **aripiprazole (oral) vs. olanzapine** When compared with olanzapine, there were no significant differences for global state (n = 1739, 11 RCTs, *very low quality evidence*); mental state using PANSS (n = 1500, 11 RCTs, *very low quality evidence*); or quality of life using the GQOLI-74 scale (n = 68, 1 RCT, *very low quality of evidence*). Significantly more people receiving aripiprazole left the study early due to any reason (n = 2331, 9 RCTs, RR 1.15 CI 1.05 to 1.25, *low quality evidence*) and significantly more people receiving olanzapine gained weight (n = 1538, 9 RCTs, RR 0.25 CI 0.15 to 0.43, *very low quality evidence*). None of the included studies provided outcome data for the comparisons of 'service use' or 'general functioning'.
	4. Anmerkungen/Fazit der Autoren Information on all comparisons is of limited quality, is incomplete and problematic to apply clinically. The quality of the evidence is all low or very low. Aripiprazole is an antipsychotic drug with an important adverse effect profile. Long-term data are sparse and there is considerable scope for another update of this review as new data emerge from ongoing larger, independent pragmatic trials.

Systematische Reviews

Dold M et al., 2016 [5]. Are all first-generation antipsychotics equally effective in treating schizophrenia? A metaanalysis of randomised, haloperidol-controlled trials	1. Fragestellung The objective of the present meta-analysis was to determine the efficacy, acceptability, and tolerability of haloperidol in comparison to all other FGAs (first-generation antipsychotics) in the pharmacotherapy of schizophrenia and related disorders based on all available randomised, controlled trials (RCTs).
	2. Methodik Population: adults with schizophrenia or related disorders (schizoaffective, schizophreniform, or delusional disorder; any diagnostic criteria) Intervention: haloperidol Komparator: orally administered FGA (direct comparison, ''head-to-head'') Endpunkt: clinically important response to treatment (PANSS or BPRS), alterations in schizophrenic symptom severity Suchzeitraum (Aktualität der Recherche): Februar 2015 (Update) Anzahl eingeschlossene Studien/Patienten (Gesamt): 79 RCTs (N=4343) Qualitätsbewertung der Studien: risk of bias'' tool described in the Cochrane Collaboration handbook
	3. Ergebnisdarstellung Eingeschlossenen Studien (grau markiert= nicht zugelassen): • Chlorpromazine (N=12, n= 518) vs. haloperidol • bromperidol (*N*= 9, *n*=498) vs. haloperidol,

	• loxapine (N=7, n=341) vs. haloperidol, • trifluoperazine (N ¼ 6, n ¼ 173) vs. haloperidol, • sulpiride (*N*=5, *n*=296) vs. haloperidol, • thiothixene (*N*=5, *n*=191) vs. haloperidol, • thioridazine (*N*=4, *n*=152) vs. haloperidol, • molindone (N=4, n=126) vs. haloperidol, • perphenazine (N=3, n=479) vs. haloperidol,, • fluphenazine (N=3,n=168) vs. haloperidol,, • pipotiazine (N=3, n=134) vs. haloperidol, • pimozide (N=3, n=72) vs. haloperidol,, • droperidol (N=2, n=86) vs. haloperidol,, • trifluperidol (N=2, n=109) vs. haloperidol,, • zuclopenthixol (N=2, n=104) vs. haloperidol,, • clopenthixol (N=2, n=92) vs. haloperidol,, • chlorprothixene (N=2, n=19) vs. haloperidol,, • levomepromazine (N=2, n=81) vs. haloperidol,, • perazine (N=2, n=82) vs. haloperidol,, • benperidol (N=1, n=33) vs. haloperidol,, • flupenthixol (N=1, n=21) vs. haloperidol,, • methylperidol (N=1, n=82) vs. haloperidol,, • nemonapride (N=1, n=167) vs. haloperidol,, • mesoridazine (N=1, n=39) vs. haloperidol,, • propericuazine (N=1, n=74) vs. haloperidol,, • thiopropazate (N=1, n=112) vs. haloperidol,, and • timiperone (N=1, n=212) vs. haloperidol,. <u>Qualitätsbewertung:</u> The risk of bias for incomplete outcome data was judged to be low in 19 studies, unclear in 37, and high in 23. Only six studies appeared to be free of selective reporting and in 35 trials, we found evidence for a high risk of other biases probably confining the study results. **Primary outcome: number of participants with clinically important response to treatment**

Antipsychotic drug	Statistics for each study					n responders / n total	
	MH risk ratio	Lower limit	Upper limit	p-Value	N	HAL	other FGA
Bromperidol	1.01	0.88	1.15	0.91	8	90 / 224	98 / 234
Chlorpromazine	1.31	0.97	1.79	0.08	7	49 / 127	40 / 146
Clopenthixol	0.74	0.49	1.10	0.14	1	17 / 33	21 / 30
Droperidol	0.87	0.73	1.04	0.12	2	25 / 43	28 / 42
Flupenthixol	0.08	0.01	1.32	0.08	1	0 / 10	6 / 11
Fluphenazine	0.78	0.37	1.65	0.51	3	9 / 68	13 / 89
Levomepromazine	0.86	0.45	1.67	0.66	2	16 / 29	27 / 42
Loxapine	1.12	0.87	1.44	0.38	3	48 / 83	42 / 79
Molindone	0.24	0.01	4.10	0.32	1	0 / 8	3 / 14
Nemonapride	0.55	0.33	0.93	0.02	1	17 / 86	29 / 81
Perazine	1.13	0.62	2.08	0.69	1	9 / 15	9 / 17
Pimozide	1.09	0.74	1.61	0.65	3	23 / 37	20 / 35
Pipotiazine	0.89	0.39	2.02	0.78	3	18 / 68	20 / 66
Sulpiride	0.83	0.50	1.39	0.48	1	15 / 37	18 / 37
Thiopropazate	1.07	0.73	1.57	0.73	1	21 / 37	26 / 49
Thioridazine	1.30	0.80	2.14	0.29	3	24 / 70	18 / 72
Thiothixene	0.82	0.47	1.44	0.49	3	47 / 80	68 / 83
Timiperone	0.80	0.57	1.11	0.18	1	38 / 106	45 / 100
Trifluoperazine	1.01	0.68	1.50	0.97	4	27 / 63	26 / 61
Zuclopenthixol	0.94	0.70	1.28	0.71	2	31 / 41	46 / 62

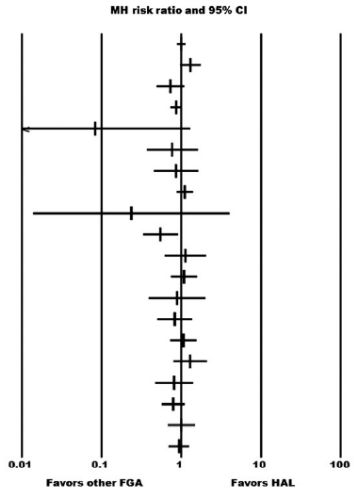


Figure 2. Effect sizes for the primary outcome clinically important response to treatment (response rates). The forest plot illustrates the Mantel–Haenszel risk ratios with the 95% confidence intervals (CI) for the pooled comparisons (haloperidol versus other first-generation antipsychotics (FGAs)). A forest plot comprising the effect sizes for all individual studies is presented in Supplementary Figure 3 (available online). Numerical values >1 indicate a higher rate of responders in the haloperidol group and <1 a higher proportion of responders in the group of the other FGA. Statistical significance can be assumed if the 95% CI does not include the value of 1 and/or the *P* value is <0.05. CI, confidence interval; FGA, first-generation antipsychotic drug; HAL, haloperidol; MH, Mantel–Haenszel; *N*, number of studies; *n*, number of participants.

secondary outcome mean change in schizophrenic symptoms measured by psychiatric rating scales (PANSS or BPRS total score).

Antipsychotic drug	Statistics for each study					
	Hedges's g	Lower limit	Upper limit	p-Value	N	n
Bromperidol	-0.16	-0.60	0.29	0.49	4	272
Chlorpromazine	-0.37	-1.01	0.27	0.26	1	37
Clopenthixol	0.26	-0.44	0.95	0.47	2	65
Flupenthixol	1.05	0.13	1.97	0.03	1	19
Fluphenazine	-0.25	-0.66	0.16	0.24	2	97
Levomepromazine	0.10	-0.50	0.70	0.75	1	41
Loxapine	3.19	0.26	6.12	0.03	3	156
Mesoridazine	-0.14	-0.75	0.48	0.67	1	39
Molindone	-0.08	-0.89	0.73	0.84	1	22
Pimozide	0.28	-0.42	0.98	0.43	1	30
Pipotiazine	0.09	-0.38	0.56	0.70	2	100
Sulpiride	-0.02	-0.58	0.53	0.93	2	47
Thiopropazate	0.48	-0.12	0.93	0.13	1	56
Thioridazine	0.34	-0.59	1.28	0.47	1	16
Thiothixene	-0.02	-0.50	0.47	0.95	2	62
Trifluoperazine	-1.34	-2.26	-0.42	0.00	1	21
Zuclopenthixol	0.11	-0.52	0.73	0.73	1	38

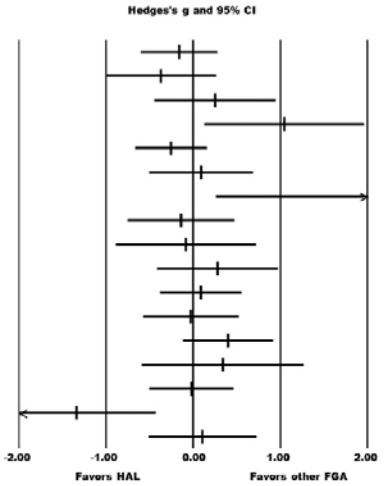


Figure 3. Effect sizes for the secondary outcome mean change in schizophrenic symptoms measured by psychiatric rating scales (PANSS or BPRS total score). The forest plot illustrates the standardised mean differences Hedges's *g* with the 95% confidence intervals (CI) for the pooled comparisons (haloperidol versus other first-generation antipsychotics (FGAs)). A forest plot comprising the effect sizes for all individual studies is presented in Supplementary Figure 4 (available online). Numerical values <0 indicate superiority of haloperidol and >0 of the other FGA. Statistical significance can be assumed if the 95% CI does not include the value of 0 and/or the *P* value is <0.05. CI, confidence interval; FGA, first-generation antipsychotic drug; HAL, haloperidol; *N*, number of studies; *n*, number of participants.

secondary outcome all-cause discontinuation (dropouts due to any reason).

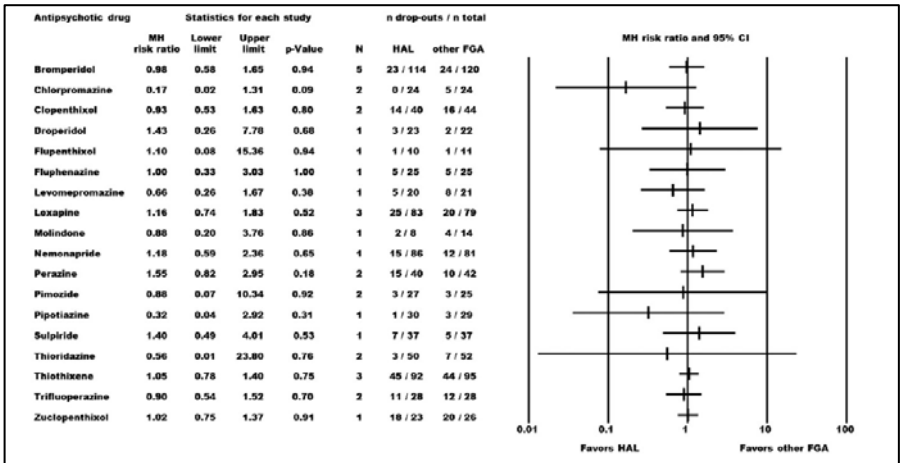


Figure 4. Effect sizes for the secondary outcome all-cause discontinuation (dropouts due to any reason). The forest plot illustrates the Mantel–Haenszel risk ratios with the 95% confidence intervals (CI) for the pooled comparisons (haloperidol versus other first-generation antipsychotics (FGAs)). A forest plot comprising the effect sizes for all individual studies is presented in Supplementary Figure 5 (available online). Numerical values >1 indicate a higher rate of dropouts in the haloperidol group compared to the control group of the other FGA. CI, confidence interval; FGA, first-generation antipsychotic drug; HAL, haloperidol; MH, Mantel–Haenszel; *N*, number of studies; *n*, number of participants.

occurrence of adverse effects

Table 1. Effect sizes for the specific adverse effects.

	At least one AE	At least one EPS	Akathisia	Dyskinesia	Dystonia	Rigour	Tardive dyskinesia	Tremor	Use of AM	Hypotension	Sedation	Weight gain
Benperidol												
Bromperidol	–	–	–	–	+	–	–	+	–	–	–	–
Chlorpromazine	–	+	–	–	–				–		–	–
Chlorprothixene												
Clopenthixol									–			
Flupenthixol		–							–			
Fluphenazine	–	–	–		–				–			
Levomepromazine								+				
Loxapine	–	–	–	–	–	–		–	–		+	
Mesoridazine		–			–				–			
Methylperidol			–			–						
Molindone			–		–	–		–	–			–
Nemonapride			–		–	–	–	–	–		–	
Perazine	+				+				+			
Perphenazine			–	–	–							
Pimozide	+	+	–	–	–	–		–	+	–	–	
Pipothiazine		–	–		–			–				–
Propericuazine												
Sulpiride	–	–	–	–					–			
Thiopropazate	–		–			–		–		–		
Thioridazine	+		–		–	–		–	–	–	–	–
Thiothixene	–	–	–	–	–	–		–				+
Timiperone		–	–	–		–						
Trifluoperazine	–	–	–						–			
Trifluperidol										–		
Zuclopenthixol									–			

This table illustrates the effect sizes (Mantel–Haenszel risk ratios) for the meta-analytic comparisons evaluating the occurrence of adverse effects; comparisons: haloperidol versus other first-generation antipsychotics (FGAs). The risk ratios (RRs) are provided with the 95% confidence intervals (CIs) for the pooled comparisons. Numerical values >1 indicate a higher occurrence of the investigated adverse effect/use of antiparkinson medication in the haloperidol group compared to the control group of the other FGAs. Statistical significance can be assumed if the 95% CI does not include the value of 1 and/or the *P* value is <0.05. Significant between-group differences are shadowed in grey in order to improve the readability of the table. An empty square indicates the absence of data for this comparison. The correspondent forest plots are displayed in Supplementary Table 1 and Figures 8 to 19 (available online). AE, adverse effect; AM, antiparkinson medication; CI, confidence interval; EPS, extrapyramidal symptom; MH, Mantel–Haenszel; *N*, number of studies; *n*, number of participants; RR, risk ratio.

4. Anmerkungen/Fazit der Autoren

Altogether, 79 RCTs with 4343 participants published between 1962 and 1999 were included. We found a significant between-group difference only between haloperidol and nemonapride, but not for the remaining 19 investigated FGAs.

There were no significant differences for discontinuation rates.

As most of the single meta-analytic comparisons can be regarded as underpowered, the evidence for the assumption of comparable efficacy of all FGAs is inconclusive. We therefore cannot confirm or reject the statements of previous narrative, unsystematic reviews in this regard.

Our findings were limited by the small sample size in the individual comparisons and the low methodological quality in many included studies.

5. *(Im Einzelfall: Kommentar zu Review /LL)*

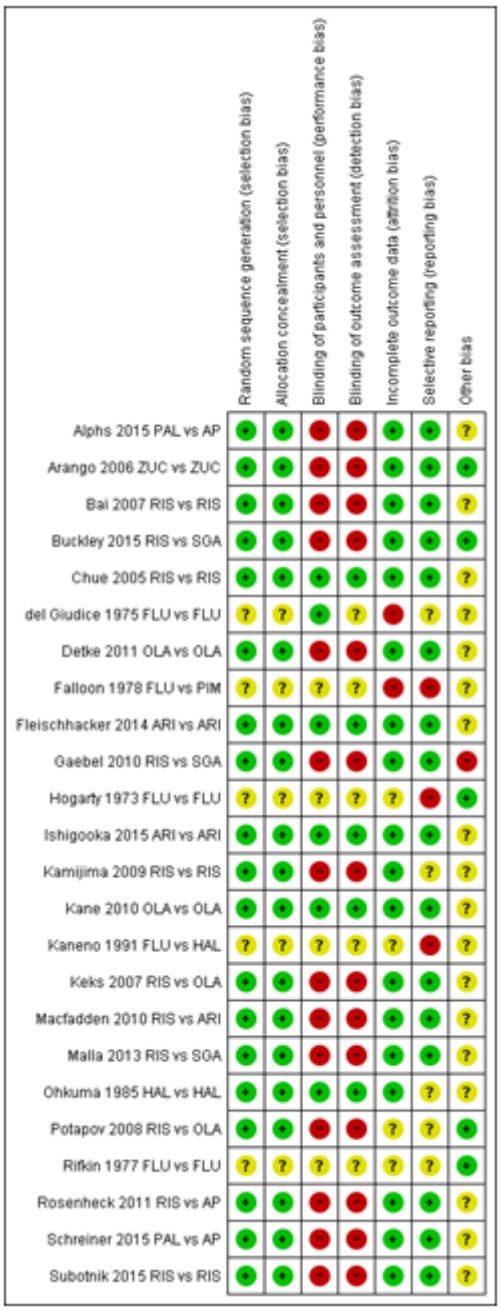
- Geringe methodische Qualität der eingeschlossenen Studien
- Vielzahl an nicht zugelassenen AM eingeschlossen – kein gemeinsamer

	Effektschätzer - Ergebnisse = comparison pairwise
Kishi T et al., 2016 [14]. Mortality Risk Associated With Long-acting Injectable Antipsychotics: A Systematic Review and Meta-analyses of Randomized Controlled Trials	1. Fragestellung We conducted a series of meta-analyses to assess whether Long-acting injectable (LAI) antipsychotics (LAI-APs) (LAI-APs) affect the mortality of patients with schizophrenia.
	2. Methodik Population: patients with schizophrenia Intervention/ Komparator: aripiprazole, bromperidol, clopenthixol, flupenthixol, fluphenazine, fluspirilene, haloperidol, iloperidone, olanzapine, oxyprothepin, paliperidone, penfluridol, perphenazine, pipothiazine, risperidone, or zuclopenthixol) AND depot, enanthate, decanoate, long-acting injection, microsphere, once monthly, palmitate, or pamoate Endpunkt: all-cause death (primary), and death due to suicide Anzahl eingeschlossene Studien/Patienten (Gesamt): 52 (n = 17 416; LAI-APs = 11 360; oral antipsychotics (OAPs) = 3910; placebo = 2146) were included in the meta-analyses) Qualitätsbewertung der Studien: Cochrane risk-of-bias criteria
	3. Ergebnisdarstellung Eingeschlossenen Studien: Studies met the inclusion criteria ($N = 151$) • Studies reported data regarding death ($N = 52$, 53 comparisons) – LAI antipsychotics versus placebo ($N = 18$) – LAI antipsychotics versus oral antipsychotics ($N = 24$) – LAI antipsychotics versus LAI antipsychotics ($N = 11$) *Hinweis: Placebovergleiche werden nicht berichtet* <u>Individual LAI-AP</u> • aripiprazole = 6 (n = 1493), • fluphenazine = 9 (n = 376), • flupentixol = 1 (n = 30), • fluphenazine/haloperidol = 1 (n = 32), • haloperidol = 4 (n = 342), • olanzapine = 3 (n = 1169), • perphenazine = 1 (n = 85), • paliperidone = 16 (n = 4092), • risperidone = 18 (n = 3562), • and zuclopenthixol = 4 (n = 179). <u>individual OAP</u> • aripiprazole = 3 (n = 669), • fluphenazine = 3 (n = 139), • haloperidol = 2 (n = 275),

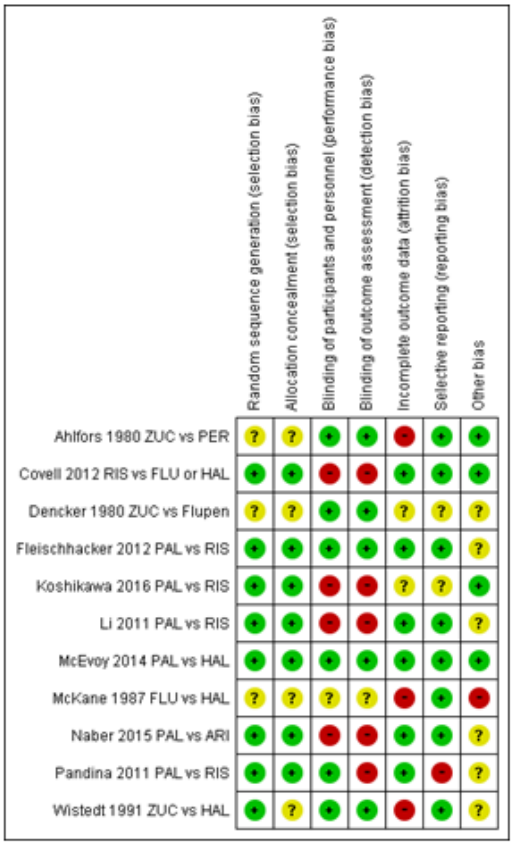
- olanzapine = 4 (n = 903),
- physicians' choice among OAPs = 3 (n = 800),
- physicians' choice among SGAs = 3 (n = 639),
- pimozide = 1 (n = 24),
- risperidone = 4 (n = 441), and
- zuclopenthixol = 1 (n = 20).

Qualitätsbewertung:

Long-acting injectable antipsychotics versus oral antipsych



Long-acting injectable antipsychotics versus long-acting injectable antipsychotics



ARI: aripiprazole, AP: antipsychotic, FLU: fluphenazine, Flupen: flupentixol, HAL: haloperidol, OLA: olanzapine, PAL: paliperidone, PBO: placebo, PER: perphenazine, PIM: pimozide, RIS: risperidone, SGA: second generation antipsychotic, ZUC: zuclopenthixol

LAI-APs vs OAPs

Neither the pooled LAI-APs nor any single individual LAI-AP (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, risperidone, and zuclopenthixol) differed from OAPs regarding the incidence of all-cause death and death due to suicide.

We did not find significant heterogeneity with respect to the primary outcome in the meta-analysis.

We did not detect publication bias (Egger's regression test: P = .949; funnel plot) or significant differences in any of the subgroup analyses between the pooled LAI-APs and OAPs

LAI-AP vs LAI-AP

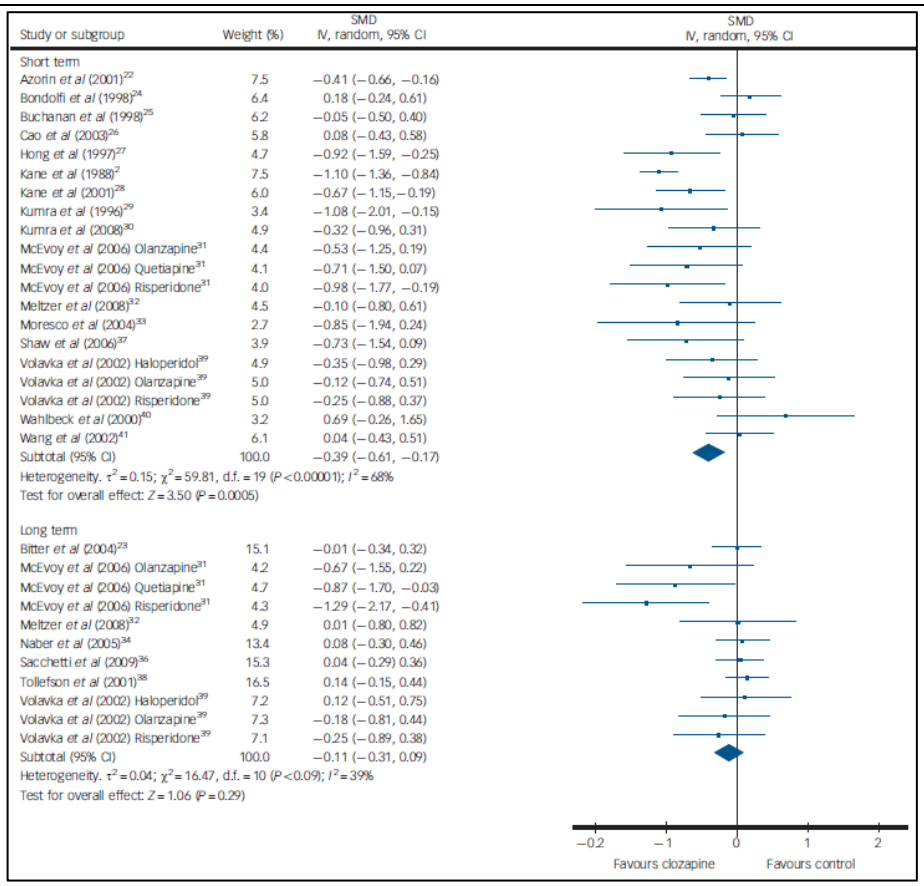
The meta-analyses of the head-to-head LAI-AP comparisons did not exhibit any significant differences in all-cause death and suicide. There were also no differences in the incidence of allcause death in any of the subgroup meta-analyses

4. Anmerkungen/Fazit der Autoren

Data were insufficient for meaningful head-to-head comparisons of individual LAI-APs. Data for individual LAI-APs vs individual OAPs were also insufficient.

Siskind D et	1. Fragestellung

al., 2016 [26]. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis	We conducted a systematic review and meta-analysis of clozapine treatment for people with treatment-refractory schizophrenia.
	2. Methodik Population: blinded. Diagnoses included schizophrenia, schizoaffective disorder or schizophreniform disorder. Participants had to have demonstrated a resistance to treatment as defined by a failure to respond to at least one trial (and preferably two) of a first- or second-generation antipsychotic of at least 6 weeks' duration at dosage equivalents greater than 600 mg chlorpromazine. Intervention: clozapine Komparator: first- or second-generation antipsychotic Endpunkt: psychotic symptoms (total, positive and negative), adverse drug reactions, study withdrawal and response to treatment Suchzeitraum (Aktualität der Recherche): Februar 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 21 RCTs (N=2364) Qualitätsbewertung der Studien: criteria adapted from Cochrane Collaboration guidelines
	3. Ergebnisdarstellung Eingeschlossene Studien: 2 der eingeschlossenen Studien vergleichen sich gegen Chlorpromzaine (=nicht zugelassen) • Hong et al 1997 • Kane et al 1988 Studiencharakteristik siehe **Anhang** Qualitätsbewertung: Study quality was fair. Seventeen papers reported adequate allocation concealment, 18 were double-blind and 3 were blinded only to assessor. Adequate random sequence generation was reported in 18 papers **Psychotic symptoms**



Change in positive symptoms.

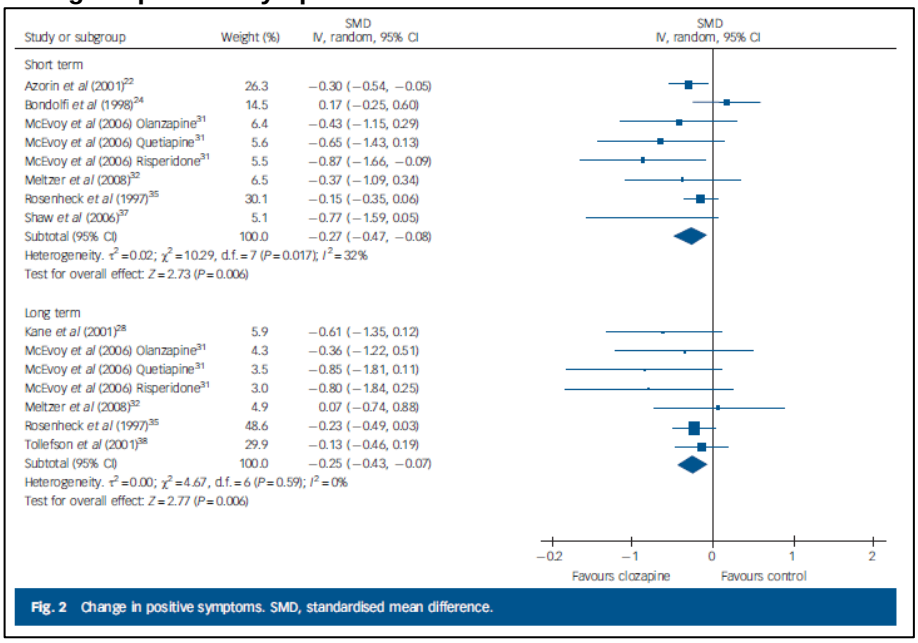


Fig. 2 Change in positive symptoms. SMD, standardised mean difference.

Change in negative symptoms

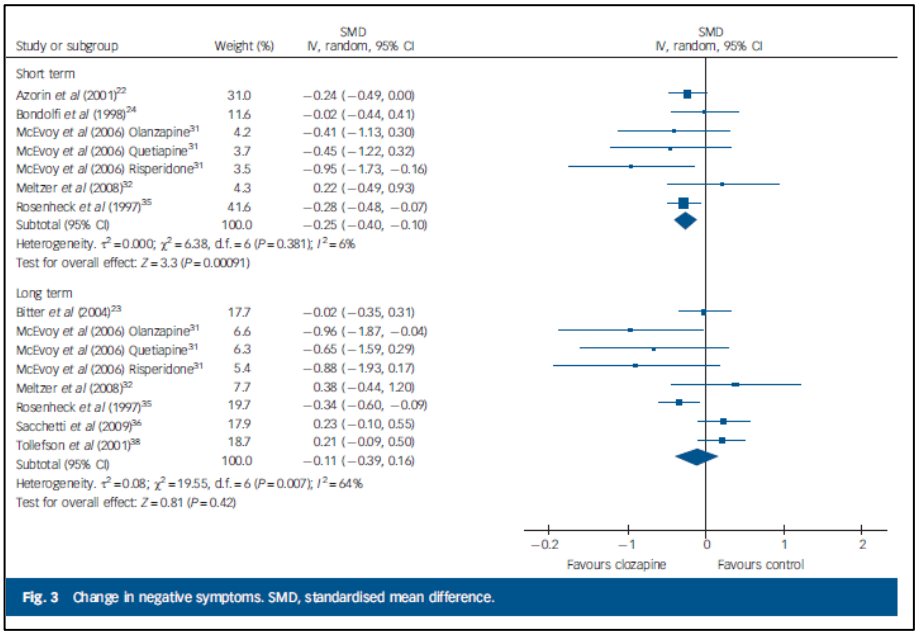


Fig. 3 Change in negative symptoms. SMD, standardised mean difference.

4. Anmerkungen/Fazit der Autoren

Our results suggest that clozapine should remain the treatment of choice for refractory schizophrenia, at least in the short term. Clozapine demonstrated superiority for positive symptoms across all time frames. Given the challenges associated with treating people with refractory disorder, our finding of a number needed to treat of 9 is moderately good.46 However, this must be balanced against numbers needed to harm that ranged from 4 for sialorrhoea to 19 for fever. In addition, if there is no meaningful improvement of symptoms or function at 6 months, our findings suggest clozapine should be stopped and consideration given to an antipsychotic with a more favourable adverse reaction profile. Pharmacological treatment should always be provided in concert with evidence-based psychosocial interventions

5. *(Im Einzelfall: Kommentar zu Review /LL)*

- Chlorpromzaine (=nicht zugelassen)
- Ergebnisse = comparison pairwise

Zhao YJ et al., 2016 [28].

Long-term antipsychotic treatment in schizophrenia: systematic review and network meta-analysis of randomised controlled trials

1. Fragestellung

To evaluate the comparative long-term effectiveness of antipsychotic drugs.

2. Methodik

Population: clinically stable patients diagnosed with schizophrenia

Intervention: antipsychotic monotherapy for relapse prevention

Komparator: aktiver Komperator oder Placebo

Endpunkt: relapse rates, drop-out rates, adverse effects

Suchzeitraum (Aktualität der Recherche): 2009-2015

Anzahl eingeschlossene Studien/Patienten (Gesamt): 56 RCTs (N=10177)

Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool

3. Ergebnisdarstellung

Hinweis: Placebovergleiche werden nicht berichtet

Eingeschlossenen Studien (grau markiert= nicht zugelassen):

Included trials involved 18 antipsychotic drug products: amisulpride, aripiprazole, chlorpromazine, flupenthixol decanoate (flupenthixol LAI), fluphenazine decanoate (fluphenazine LAI), haloperidol, haloperidol decanoate (haloperidol LAI), olanzapine, paliperidone, paliperidone palmitate (paliperidone LAI), pipothiazine palmitate (pipothiazine LAI), quetiapine, risperidone, risperidone LAI, sulpiride, trifluoperazine, ziprasidone and zuclopenthixol decanoate (zuclopenthixol LAI).

Qualitätsbewertung:

One study (2% of all reports) had high risk of bias in random sequence generation, 10 (18%) appear to have had adequate sequence generation and 4 (7%) had apparently adequate allocation concealment. Most studies (47/56, 84%) were nominally double-blind and 21 (38%) tested and confirmed the success of blinding.

no significant inconsistency between direct and indirect evidence was identified within the evidence network as a whole (P=0.14)

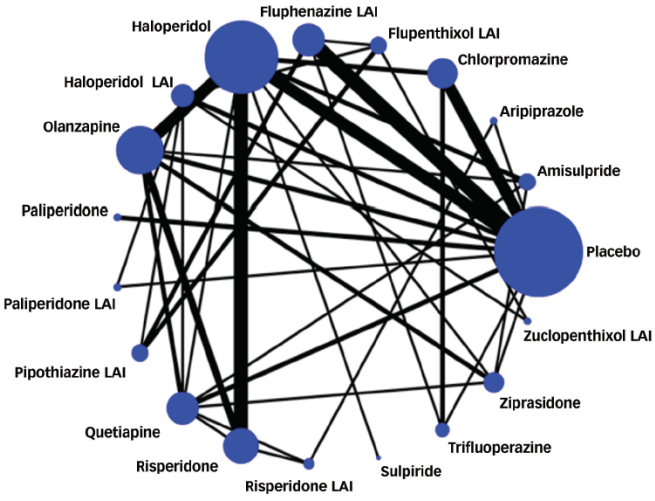


Fig. 2 Network of all direct and indirect comparisons between antipsychotics. LAI, long-acting injection.

Efficacy

Olanzapine was significantly more effective than chlorpromazine (OR=0.35, 95% CI 0.14–0.88) and haloperidol (OR=0.50, 95% CI 0.30–0.82) in reducing relapses, and fluphenazine LAI was superior to chlorpromazine (OR=0.31, 95% CI 0.11–0.88

The top five drugs ranked by their SUCRA values were zuclopenthixol LAI (0.85), fluphenazine LAI (0.78), olanzapine (0.76), pipothiazine LAI (0.68) and paliperidone (0.67). Findings for relapse prevention were consistent when we analysed oral and long-acting agents separately

Fourteen trials (2886 participants) were included for the network meta-analysis of hospital admissions. Oral agents including amisulpride, haloperidol, olanzapine, quetiapine and ziprasidone were significantly more effective in reducing readmissions than placebo, but aripiprazole, chlorpromazine, paliperidone, trifluoperazine did not differ from placebo

In reducing readmission, olanzapine and ziprasidone were significantly more effective than haloperidol or quetiapine; amisulpride, fluphenazine LAI, haloperidol, olanzapine, risperidone LAI and ziprasidone all were superior to aripiprazole, and ziprasidone alone outperformed chlorpromazine and

	trifluoperazine. **Safety and tolerability** In general, long-acting agents tended to be better tolerated than oral agents, but not statistically significant. Olanzapine was associated with less all-cause discontinuation than quetiapine (OR=0.44, 95% CI 0.22–0.88) or haloperidol (OR=0.49, 95% CI 0.29–0.80), whereas zuclopenthixol LAI yielded less all-cause discontinuation than chlorpromazine (OR=0.12 (0.01–0.97)), quetiapine (OR=0.14 (0.02–0.88)) or sulpiride (OR=0.09 (0.01–0.97)). Olanzapine was associated with less risk of EPS than other agents except aripiprazole, flupenthixol LAI, quetiapine and zuclopenthixol LAI. As expected, quetiapine had less reported EPS than fluphenazine LAI, haloperidol, haloperidol LAI, paliperidone, paliperidone LAI, pipothiazine LAI, trifluoperazine and ziprasidone. Fluphenazine LAI, haloperidol, haloperidol LAI and trifluoperazine were associated with significantly more EPS than several other agents. Only 15 trials (5147 participants) were synthesised for weight gain. Olanzapine produced significantly more weight gain than amisulpride, haloperidol, quetiapine, risperidone, ziprasidone and placebo. Ziprasidone was associated with less weight gain than amisulpride, quetiapine and risperidone. Amisulpride, haloperidol, olanzapine, quetiapine, ziprasidone and paliperidone LAI were not associated with higher rate of glucose intolerance than placebo or as compared with each other amisulpride, risperidone and risperidone LAI produced hyperprolactinaemia more often than haloperidol, olanzapine, quetiapine or ziprasidone. no differences between antipsychotics and placebo or among antipsychotics in terms of death or suicide attempt
	4. Anmerkungen/Fazit der Autoren In conclusion, relatively minor differences in relapse prevention were observed among most antipsychotics, although olanzapine and fluphenazine decanoate were associated with particularly lower relapse rates. These relative apparent benefits need to be weighed against the risks of adverse effects of all antipsychotic drugs, notably of weight gain and metabolic syndrome with olanzapine, and EPS with fluphenazine decanoate.
Oya K et al., 201 [21]. Efficacy and tolerability of aripiprazole once monthly for schizophrenia: a systematic review and meta-analysis of randomized controlled trials	1. Fragestellung We thus performed a systematic review and meta-analysis of four RCTs of AOM (aripiprazole once monthly) to assess its efficacy and tolerability (as indicated by discontinuation rate, EPS (extrapyramidal symptom), and individual AEs).
	2. Methodik Population: patients with schizophrenia Intervention: AOM (aripiprazole once monthly) Komparator: placebo, OA (Oral aripiprazole), and/or AOM dosing Endpunkt: efficacy and safety Suchzeitraum (Aktualität der Recherche): Juni 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 RCTs (N=1860) Qualitätsbewertung der Studien: Cochrane risk-of-bias criteria

	3. Ergebnisdarstellung *Hinweis: Placebovergleiche werden nicht berichtet* Eingeschlossenen Studien: Two were placebo-controlled studies, one OA controlled, and the other compared AOM, OA, and AOM-50 mg (defined as placebo as this dose is subthreshold) Qualitätsbewertung: All four were of high methodological quality based on Cochrane Risk of Bias Criteria (they were double-blind RCTs and contained the required study design detail). **Efficacy - AOM vs OA** With respect to psychiatric symptoms, AOM was comparable to OA for the reduction of PANSS total score (SMD =-0.08, 95% CI =-0.31 to 0.14, *P*=0.46, *I*2=69%, two comparisons, n=984), CGI-S score (SMD =-0.09, 95% CI =-0.40 to 0.22, *P*=0.56, *I*2=83%, two comparisons, n=977), and CGI-I score (SMD =-0.17, 95% CI =-0.49 to 0.16, *P*=0.31, *I*2=85%, two comparisons, n=986). With respect to patients' outcomes, AOM was comparable to OA regarding observed relapse rate (RR =1.03, 95% CI =0.66–1.60, *P*=0.90, *I*2=0%, two comparisons, n=986) and proportion of remitters (RR =1.08, 95% CI =0.92–1.28, *P*=0.34, *I*2=0%, two comparisons, n=775). **Safety and tolerability - AOM vs OA** AOM was superior to OA regarding all-cause discontinuation (RR =0.78, 95% CI =0.64–0.95, P=0.01, I2=0%, two comparisons, n=986, NNH =14). AOM and OA did not differ in discontinuation due to AEs (RR =0.75, 95% CI =0.45–1.24, P=0.27, I2=0%, two comparisons, n=986), discontinuation due to inefficacy (RR =0.93, 95% CI =0.61–1.42, P=0.73, I2=0%, two comparisons, n=986), and discontinuation due to death (RR =0.62, 95% CI =0.08–5.05, P=0.66, I2=0%, two comparisons, n=986). Regarding EPS, AOM, and OA did not differ in AIMS score (SMD =-0.06, 95% CI =-0.38 to 0.26, P=0.73, I2=78%, two comparisons, n=680) or BARS score (SMD =0.25, 95% CI =-0.24 to 0.74, P=0.31, I2=90%, two comparisons, n=680). AOM did not increase the incidence of weight gain compared to OA (RR =0.97, 95% CI =0.46–2.06, P=0.94, I2=68%, two comparisons, n=986), but mean change in body weight at last visit was lower in the AOM group (SMD =-0.16, 95% CI =-0.29 to -0.02, P=0.02, I2=0%, two comparisons, n=847). There were no significant differences in AEs, including akathisia, injection site pain, insomnia, nasopharyngitis, and suicide ideation, between AOM and OA groups, while incidence of injection site pain was marginally higher in the AOM group (RR =2.00, 95% CI =0.92–4.36, P=0.08, I2=65%, two comparisons, n=986).
	4. Anmerkungen/Fazit der Autoren In conclusion, our results suggest that AOM is a well-tolerated treatment and improves the psychopathology of schizophrenia. Future research should investigate the long-term efficacy and generate more safety data for AOM.
Samara MT et al., 2016 [23]. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-	1. Fragestellung To integrate all the randomized evidence from the available antipsychotics used for treatment-resistant schizophrenia by performing a network meta-analysis. What is the most effective and acceptable antipsychotic for treatment-resistant schizophrenia?
	2. Methodik

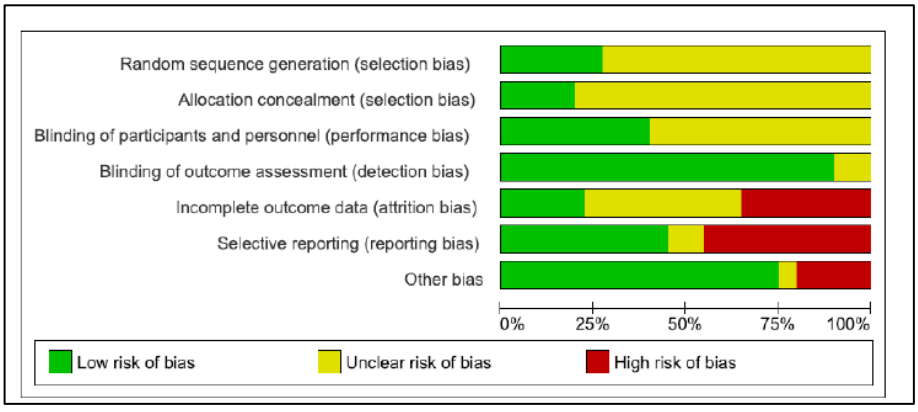
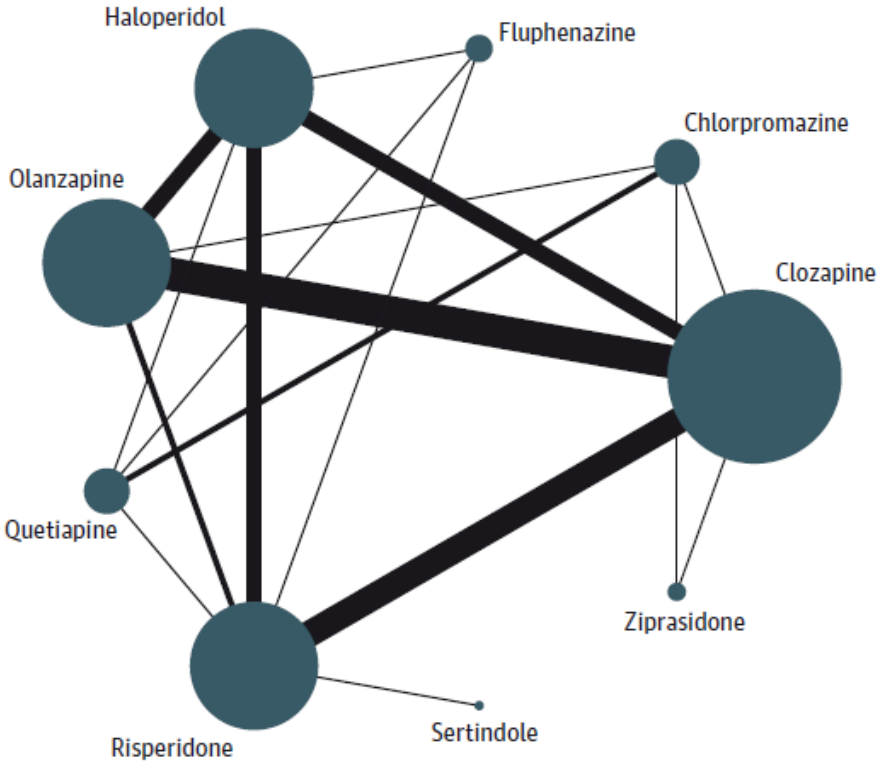
Resistant Schizophrenia A Network Meta-analysis	Population: patientswith a treatment-resistant form of schizophrenia, schizophreniform disorder, or schizoaffective disorder Intervention: antipsychotics, at any dose and in any form of administration Komparator: another antipsychotic or placebo Endpunkt: mean change from baseline to end point in overall symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS); response to treatment that was defined primarily as at least a 20% reduction of PANSS or Brief Psychiatric Rating Scale score or at least minimal improvement on the Clinical Global Impressions Scale; change in positive and negative symptoms of schizophrenia, dropoutsowing toanyreason (all-cause discontinuation), dropouts owing to inefficacy of treatment, the occurrence of important adverse effects (ie,weight gain, extrapyramidal symptoms, and sedation), quality of life, ability to work, and economic outcomes. Suchzeitraum (Aktualität der Recherche): Juni 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 40 RCTs (N=5172) Qualitätsbewertung der Studien: Cochrane Collaboration's risk-of-bias tool.
	3. Ergebnisdarstellung *Hinweis: Placebovergleiche werden nicht berichtet* Eingeschlossenen Studien (grau markiert= nicht zugelassen): The drug involved in most comparisons was clozapine (20 of 40 trials) followed by haloperidol (15 of 40 trials), olanzapine (14 of 40 trials), and risperidone (12 of 40 trials), whereas few trials were available for most other drugs. Three antipsychotics (aripiprazole, perphenazine, and thiothixene hydrochloride) Qualitätsbewertung: 

Figure 2. Network Plot for Mean Change in Overall Symptoms of Schizophrenia



The size of the nodes corresponds to the number of trials that study the treatments. Directly comparable treatments are linked with a line; the thickness of the line corresponds to the number of trials that assess the comparison.

mean change from baseline to end point in overall symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS)

pairwise meta-analytic comparisons

only olanzapine was significantly better than haloperidol (SMD,−0.29, corresponding to−6.08 PANSS points; 95% CRI, −0.53 to −0.06) based on 4 studies (693 participants).

NMA

Olanzapine was significantly more effective than quetiapine fumarate (SMD, −0.29, corresponding to −6.08 PANSS points; CRI, −0.56 to −0.02), haloperidol (SMD, −0. 29, corresponding to −6.08 PANSS points; CRI, −0.44 to −0.13), and sertindole (SMD, −0.46, corresponding to −9.64 PANSS points; 95%CRI,−0.80 to −0.06); clozapine was significantly more effective than haloperidol (SMD,−0.22, corresponding to−4. 61PANSS points; 95%CRI,−0.38to−0.07) and sertindole (SMD, −0.40, corresponding to −8.39 PANSS points; 95% CRI,−0.74to−0.04);and risperidone was significantly more effective than sertindole (SMD, −0.32, corresponding to −6.71 PANSS points; 95% CRI, −0.63 to −0.01).

In terms of rankings, olanzapine was ranked first, followed by ziprasidone and clozapine, but results for ziprasidone were based on only 2 studies (n = 453) and did not show a significant difference compared with any other antipsychotic.

	Positive and Negative Symptoms *pairwise meta-analytic comparisons* *Positive Symptoms:* only risperidone was statistically significantly better than fluphenazine hydrochloride and quetiapine (SMDs, −0.73 [95%CRI, −1.48 to −0.02] and −0.93 [95%CRI, −1.72 to −0.11], respectively; corresponding to −5.16 and −6.57 PANSS points, respectively) based on a single small trial with 38 participants *Negative Symptoms:* Olanzapine was significantly more efficacious than risperidone (SMD,−0.43, corresponding to−2.42 PANSS points; 95%CRI, −0.84 to−0.02) and haloperidol (SMD, −0.26, corresponding to −1.46 PANSS points; 95%CRI, −0.50 to −0.02). *NMA* *Positive Symptoms:* Risperidone, clozapine, and olanzapinewere significantly more efficacious than quetiapine (SMDs, −0.43 [95% CRI, −0.81 to −0.09], −0.40 [95% CRI, −0.75 to −0.09], and −0.33 [95%CRI, −0.67 to −0.01], respectively, corresponding to −3.04, −2.83, and −2.33 PANSS points, respectively). Inaddition, risperidone and clozapine were significantly more efficacious than haloperidol (SMDs,−0.29[95%CRI,−0.54 to−0.07]and−0.27[95%CRI,−0.46to−0.09], respectively, corresponding to −2.05 and −1.91 PANSS points, respectively). *Negative Symptoms:* In the NMA, olanzapine was better than clozapine (SMD, −0.14, corresponding to −0.79 PANSS points; 95%CRI, -0.30 to-0.01), risperidone (SMD,−0.24, corresponding to−1.35 PANSS points; 95% CRI, −0.44 to −0.02), haloperidol (SMD, −0.24, corresponding to −1.35 PANSS points; 95%CRI, −0.40 to−0.04), chlorpromazine (SMD,−0.26, corresponding to−1.46 PANSS points; 95%CRI, −0.51 to −0.02), and sertindole (SMD, −0.44, corresponding to −2.48 PANSS points; 95%CRI, −0.81 to −0.08). Ziprasidone was better than chlorpromazine (SMD, −0.26, corresponding to −1.46 PANSS points; 95% CRI, −0.53 to −0.04) and sertindole (SMD, −0.44, corresponding to −2.48 PANSS points; 95% CRI, −0.88 to −0.01). **Categorical Response to Treatment** *pairwise meta-analytic comparisons* In the pairwise comparisons, findings were significantly better for risperidone (OR,9.68; 95% CRI, 1.11-183.46) and clozapine (OR 1.86; 95% CRI, 1.01-4.00) compared with haloperidol. *NMA* In the network comparisons, significantly better results were foundfor risperidone (OR, 2.27; 95% CRI, 1.11-4.73), clozapine (OR, 2.09; 95% CRI, 1.26-3.82), and olanzapine (OR, 2.00; 95%CRI, 1.16-3.76) compared with haloperidol (NNTBs, 7, 8, and 8, respectively). **Discontinuation** *pairwise meta-analytic comparisons* In pairwise comparisons, only olanzapine was better than haloperidol (OR, 0.52; 95%CRI, 0.24-0.97). In the NMA, no difference among antipsychotics was found apart fromolanzapine being better than haloperidol (OR,0.56; 95% CRI,0.33-0.87; NNTH, 9)andfluphenazine (OR,0.24;95%CRI, 0.03-0.87; NNTH, 5). In pairwise comparisons of discontinuation owing to inefficacy, clozapine was better than risperidone (OR, 0.32; 95% CRI, 0.14-0.81) and haloperidol (OR, 0.18; 95% CRI, 0.08-0.46), and olanzapine was better than haloperidol (OR, 0.32; 95% CRI, 0.10-0.99).

NMA

In the NMA, clozapine was better than risperidone, quetiapine, haloperidol, and fluphenazine (OR range, 0.44 [95% CRI, 0.19-0.91] to 0.08 [95% CRI, 0.01-0.35]; NNTH range, 6-10); chlorpromazine and olanzapine were better than haloperidol and fluphenazine (OR range, 0.04 [95% CRI, 0.01-0.76] to 0.27 [95% CRI, 0.11-0.60]; NNTH range, 5-7); and risperidone was better than fluphenazine (OR, 0.19; 95% CRI, 0.02-0.81; NNTH, 7)

Adverse Events

eTable 6. Extrapyramidal side-effects

CLO	0.71 (0.07, 7.31)	0.98 (0.07, 13.46)	-	**0.09 (0.01, 0.40)**	-	-
0.92 (0.16, 2.69)	ZIP	-	-	-	-	-
0.55 (0.08, 1.85)	1.02 (0.07, 5.18)	OLA	1.16 (0.08, 17.22)	0.30 (0.02, 3.77)	-	-
0.38 (0.03, 1.48)	0.18 (0.03, 3.52)	0.46 (0.13, 3.09)	QUE	2.25 (0.10, 52.93)	0.73 (0.04, 13.12)	0.14 (0.01, 1.97)
0.15 (0.04, 0.39)	0.12 (0.03, 1.08)	0.24 (0.08, 1.22)	0.40 (0.13, 2.22)	RIS	0.36 (0.02, 6.99)	0.33 (0.01, 7.06)
0.20 (0.01, 1.23)	0.04 (0.01, 2.22)	0.11 (0.02, 2.99)	0.66 (0.06, 3.22)	**1.35 (0.09, 0.68)**	FLUPH	-
0.07 (0.01, 0.31)	**0.03 (0.01, 0.68)**	**0.06 (0.01, 0.75)**	**0.23 (0.03, 0.77)**	0.50 (0.06, 2.03)	0.91 (0.05, 4.43)	HAL

Pairwise (upper triangle) and NMA (lower triangle) results for the outcome 'Extrapyramidal side-effects'. For pairwise results, odds ratio values lower than 1 indicate that in the treatment specified in the row less patients were treated with Antiparkinson medication. For NMA results, odds ratio values lower than 1 indicate that in the treatment specified in the column less patients were treated with Antiparkinson medication. Bold underlined results indicate statistical significance. The overall heterogeneity (τ) is equal to 0.90 for pairwise and equal to 0.51 for NMA results.

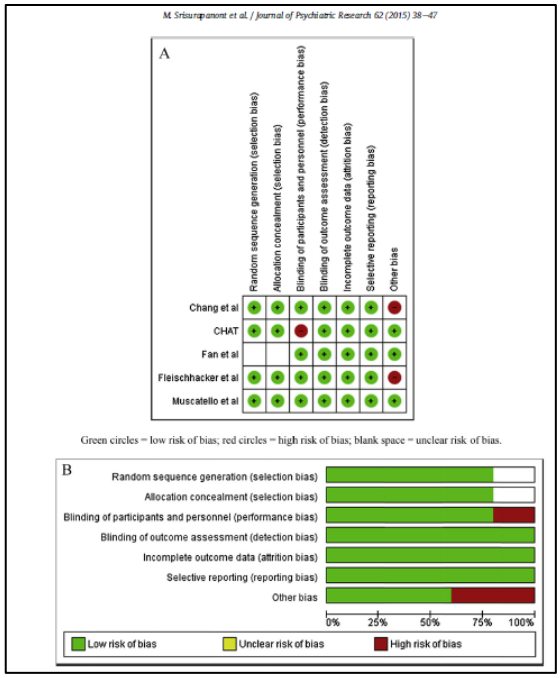
eTable 5. Weight gain

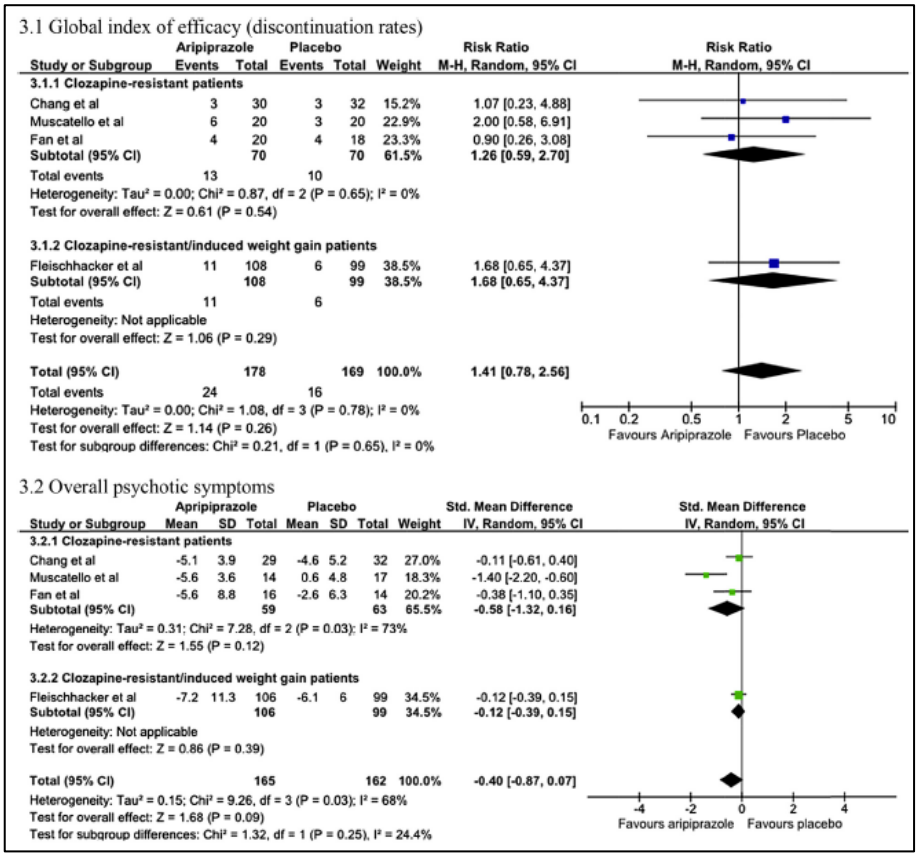
HAL	-	-	-0.14 (-1.05, 0.78)	-	**-1.03 (-2.01, -0.04)**	-	-0.66 (-1.37, 0.03)	**-1.31 (-2.01, -0.61)**
-0.04 (-1.04, 0.98)	FLUPH	-	-0.15 (-1.32, 1.01)	-	-0.43 (-1.60, 0.74)	-	-	-
-0.05 (-1.04, 0.97)	-0.02 (-1.31, 1.31)	ZIP	-	-0.21 (-1.13, 0.70)	-	-	-0.72 (-1.66, 0.22)	-
-0.16 (-0.79, 0.46)	-0.13 (-1.14, 0.88)	-0.11 (-1.23, 0.97)	QUE	-	-0.07 (-1.24, 1.10)	-	-	-0.85 (-1.91, 0.22)
-0.26 (-1.56, 1.08)	-0.23 (-1.78, 1.35)	-0.21 (-1.07, 0.65)	-0.10 (-1.48, 1.32)	CPZ	-	-	-	-
-0.31 (-0.86, 0.24)	-0.28 (-1.18, 0.62)	-0.26 (-1.25, 0.70)	-0.15 (-0.81, 0.52)	-0.05 (-1.36, 1.23)	RIS	-0.15 (-1.07, 0.77)	**-0.53 (-1.02, -0.01)**	-0.63 (-1.36, 0.11)
-0.46 (-1.48, 0.56)	-0.42 (-1.67, 0.82)	-0.40 (-1.72, 0.88)	-0.29 (-1.38, 0.80)	-0.19 (-1.76, 1.35)	-0.14 (-1.00, 0.71)	SER	-	-
-0.78 (-1.25, -0.28)	-0.74 (-1.70, 0.23)	-0.73 (-1.62, 0.15)	-0.62 (-1.26, 0.05)	-0.52 (-1.75, 0.70)	**-0.47 (-0.87, -0.04)**	-0.32 (-1.26, 0.64)	CLO	-0.18 (-0.60, 0.19)
-0.99 (-1.47, -0.51)	-0.95 (-1.93, 0.02)	**-0.94 (-1.90, -0.01)**	**-0.83 (-1.46, -0.19)**	-0.73 (-2.03, 0.53)	**-0.68 (-1.14, -0.22)**	-0.53 (-1.51, 0.43)	-0.21 (-0.57, 0.12)	OLA

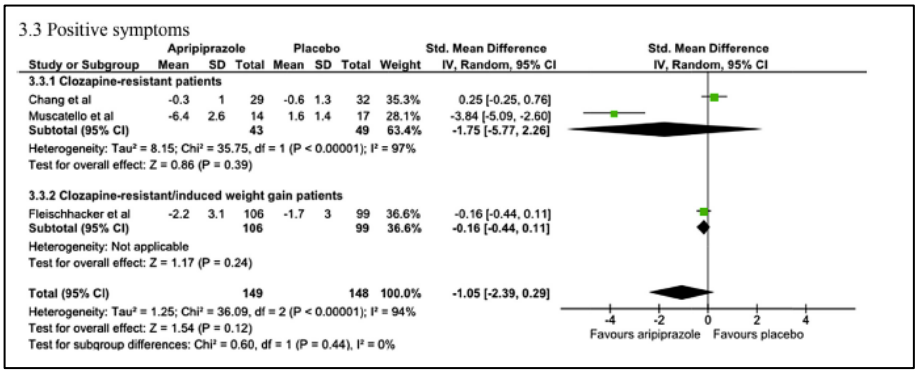
Pairwise (upper triangle) and NMA (lower triangle) results for the outcome 'Weight gain'. For pairwise results, standardized mean difference values lower than 0 indicated that the treatment specified in the row is better. For NMA results, standardized mean difference values lower than 0 indicated that the treatment specified in the column is better. Bold underlined results indicate statistical significance. The overall heterogeneity (τ) is equal to 0.42 for pairwise and equal to 0.40 for NMA results.

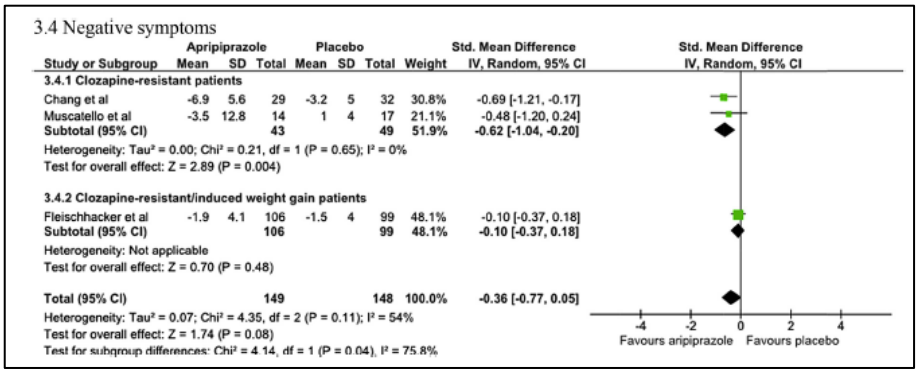
Quality of life

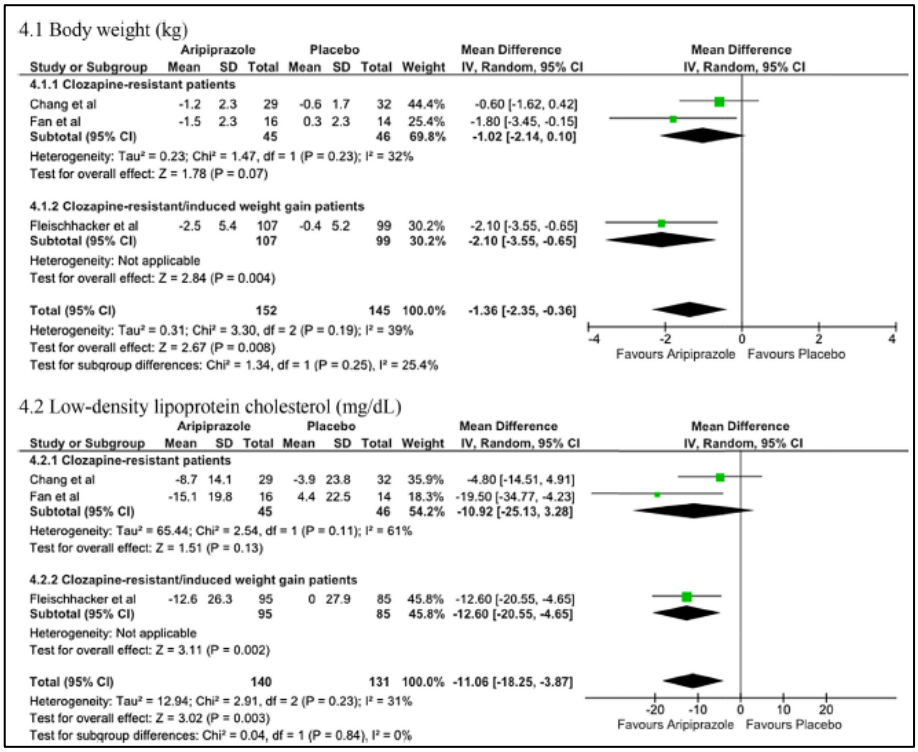
	eTable 8. Quality of life **Quality of life** **Comparison** / **Estimate(95% CI)** QUE vs. CPZ: 0.21 (-1.91, 2.31) OLA vs. HAL: -0.01 (-2.14, 2.13) QUE vs. FLUPH: -0.21 (-2.4, 2.01) RIS vs. FLUPH: -0.23 (-2.45, 1.98) CLO vs. HAL: -0.23 (-2.36, 1.91) Pairwise results for the outcome 'Quality of life'. Standardized mean difference values lower than 0 indicate that first treatment is better. Bold underlined results indicate statistical significance. The overall heterogeneity (τ) is equal to 0.78. Only 5 studies provided data on quality of life. The pairwise meta-analysis did not indicate any significant difference among antipsychotics, whereas conducting an NMA was not feasible.
	4. Anmerkungen/Fazit der Autoren A pattern of superiority for olanzapine, clozapine, and risperidone was seen in other efficacy outcomes, but results were not consistent and effect sizes were usually small. In addition, relatively few RCTs were available for antipsychotics other than clozapine, haloperidol, olanzapine, and risperidone. The most surprising finding was that clozapine was not significantly better than most other drugs. At present, insufficient blinded evidence exists on which antipsychotic is more efficacious for patients with treatment resistant schizophrenia. Clozapine's superiority over the FGAs has been demonstrated repeatedly, which establishes clozapine as the standard treatment in this specific population, but evidence from blinded RCTs for the comparison of clozapine with other SGAs is lacking. Our analysis suggests that more trials comparing clozapine with other SGAs in patients with more severe illness and using high clozapine doses are warranted. Moreover, the evidence on antipsychotics other than clozapine, haloperidol, olanzapine, and risperidone is scarce, and their results can change if further studies become published.
Srisurapanont M et al., 2015 [27]. Efficacy and safety of aripiprazole augmentation of clozapine in schizophrenia: A systematic review and meta-analysis of randomized-controlled trials	1. Fragestellung we proposed to carry out a systematic review of randomized-controlled trials to determine the efficacy and safety of aripiprazole augmentation for patients with clozapine-resistant schizophrenia or clozapine related cardiometabolic risk.
	2. Methodik Population: patients with schizophrenia who had an unsatisfactory response to clozapine, including not fully responsive and having cardiometabolic risk. Intervention: Aripiprazole Komparator: placebo and/or other pharmacological agents as an agent adjunct to clozapine Endpunkt: efficacy, cardiometabolic indices, and adverse effects Suchzeitraum (Aktualität der Recherche): Juli 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 RCTs → 4 RCTs für Meta-Analyse Qualitätsbewertung der Studien: risk of bias by using criteria described in the Cochrane Handbook for Systematic Reviews of Interventions v.5.1.0
	3. Ergebnisdarstellung

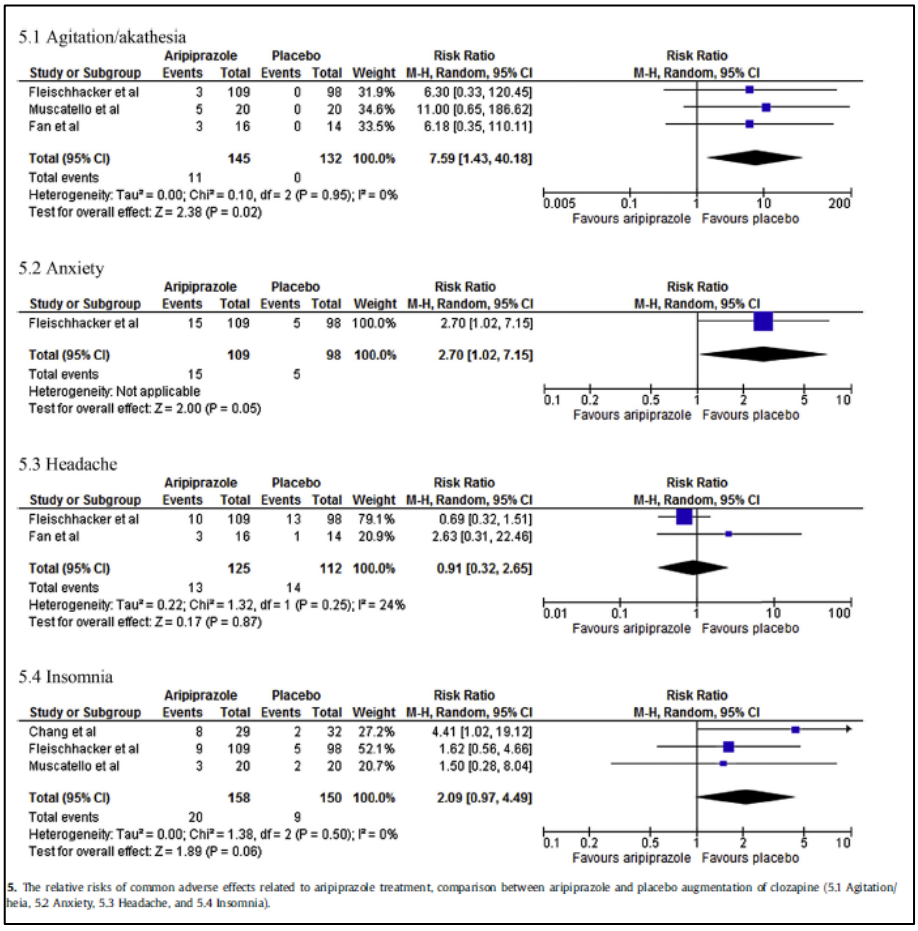
	Eingeschlossenen Studien Four RCTs were short-term (8-24 weeks) comparison of aripiprazole and placebo in combination with clozapine (Chang et al., 2008; Fan et al., 2013; Fleischhacker et al., 2010; Muscatello et al., 2011) (see Table 1). The data of these four short-term RCTs (n= 347) were quantitatively synthesized. The other long-term RCT (1 year, n=106, Clozapine Haloperidol Aripiprazole Trial or CHAT) was presented separately because it was clearly unique by comparing aripiprazole and haloperidol in clozapine-resistant schizophrenia (Barbui et al., 2011; Cipriani et al., 2013). Qualitätsbewertung: 


3.1 Global index of efficacy (discontinuation rates)
Aripiprazole
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
3.1.1 Clozapine-resistant patients
Chang et al 3 30 3 32 15.2% 1.07 [0.23, 4.88]
Muscatello et al 6 20 3 20 22.9% 2.00 [0.58, 6.91]
Fan et al 4 20 4 18 23.3% 0.90 [0.26, 3.08]
Subtotal (95% CI) 70 70 61.5% 1.26 [0.59, 2.70]
Total events 13 10
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)
3.1.2 Clozapine-resistant/induced weight gain patients
Fleischhacker et al 11 108 6 99 38.5% 1.68 [0.65, 4.37]
Subtotal (95% CI) 108 99 38.5% 1.68 [0.65, 4.37]
Total events 11 6
Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)
Total (95% CI) 178 169 100.0% 1.41 [0.78, 2.56]
Total events 24 16
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 3 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.26)
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favours Aripiprazole Favours Placebo
3.2 Overall psychotic symptoms
Apripiprazole
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
3.2.1 Clozapine-resistant patients
Chang et al -5.1 3.9 29 -4.6 5.2 32 27.0% -0.11 [-0.61, 0.40]
Muscatello et al -5.6 3.6 14 0.6 4.8 17 18.3% -1.40 [-2.20, -0.60]
Fan et al -5.6 8.8 16 -2.6 6.3 14 20.2% -0.38 [-1.10, 0.35]
Subtotal (95% CI) 59 63 65.5% -0.58 [-1.32, 0.16]
Heterogeneity: Tau² = 0.31; Chi² = 7.28, df = 2 (P = 0.03); I² = 73%
Test for overall effect: Z = 1.55 (P = 0.12)
3.2.2 Clozapine-resistant/induced weight gain patients
Fleischhacker et al -7.2 11.3 106 -6.1 6 99 34.5% -0.12 [-0.39, 0.15]
Subtotal (95% CI) 106 99 34.5% -0.12 [-0.39, 0.15]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)
Total (95% CI) 165 162 100.0% -0.40 [-0.87, 0.07]
Heterogeneity: Tau² = 0.15; Chi² = 9.26, df = 3 (P = 0.03); I² = 68%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Chi² = 1.32, df = 1 (P = 0.25), I² = 24.4%
-4 -2 0 2 4
Favours aripiprazole Favours placebo


3.3 Positive symptoms
Apripiprazole
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
3.3.1 Clozapine-resistant patients
Chang et al -0.3 1 29 -0.6 1.3 32 35.3% 0.25 [-0.25, 0.76]
Muscatello et al -6.4 2.6 14 1.6 1.4 17 28.1% -3.84 [-5.09, -2.60]
Subtotal (95% CI) 43 49 63.4% -1.75 [-5.77, 2.26]
Heterogeneity: Tau² = 8.15; Chi² = 35.75, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 0.86 (P = 0.39)
3.3.2 Clozapine-resistant/induced weight gain patients
Fleischhacker et al -2.2 3.1 106 -1.7 3 99 36.6% -0.16 [-0.44, 0.11]
Subtotal (95% CI) 106 99 36.6% -0.16 [-0.44, 0.11]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.17 (P = 0.24)
Total (95% CI) 149 148 100.0% -1.05 [-2.39, 0.29]
Heterogeneity: Tau² = 1.25; Chi² = 36.09, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.54 (P = 0.12)
Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² = 0%
-4 -2 0 2 4
Favours aripiprazole Favours placebo


3.4 Negative symptoms
Apripiprazole
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
3.4.1 Clozapine-resistant patients
Chang et al -6.9 5.6 29 -3.2 5 32 30.8% -0.69 [-1.21, -0.17]
Muscatello et al -3.5 12.8 14 1 4 17 21.1% -0.48 [-1.20, 0.24]
Subtotal (95% CI) 43 49 51.9% -0.62 [-1.04, -0.20]
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.89 (P = 0.004)
3.4.2 Clozapine-resistant/induced weight gain patients
Fleischhacker et al -1.9 4.1 106 -1.5 4 99 48.1% -0.10 [-0.37, 0.18]
Subtotal (95% CI) 106 99 48.1% -0.10 [-0.37, 0.18]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
Total (95% CI) 149 148 100.0% -0.36 [-0.77, 0.05]
Heterogeneity: Tau² = 0.07; Chi² = 4.35, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Chi² = 4.14, df = 1 (P = 0.04), I² = 75.8%
-4 -2 0 2 4
Favours aripiprazole Favours placebo





5. The relative risks of common adverse effects related to aripiprazole treatment, comparison between aripiprazole and placebo augmentation of clozapine (5.1 Agitation/heia, 5.2 Anxiety, 5.3 Headache, and 5.4 Insomnia).

4. Anmerkungen/Fazit der Autoren

In conclusion, the limited data suggest that short-term aripiprazole augmentation of clozapine can minimize some cardiometabolic risk but also causes agitation/akathesia. We need more data to support its benefits in

	attenuating psychotic symptoms and its side effects of anxiety, and insomnia. Further studies on aripiprazole and other augmentation treatments that might increase the efficacy or minimize the cardiometabolic side effects of clozapine are still needed. 5. *(Im Einzelfall: Kommentar zu Review /LL)* - *Nur Placebovergleiche eingeschlossen*
Cameron C et al., 2017 [4]. Aripiprazole Lauroxil Compared with Paliperidone Palmitate in Patients with Schizophrenia: An Indirect Treatment Comparison	1. Fragestellung To indirectly compare efficacy and safety of the pivotal Aripiprazole lauroxil (AL) study with all PP studies meeting indirect comparison criteria
	2. Methodik Population: population comprised adults with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, criteria and who were experiencing an acute exacerbation. Intervention: Aripiprazole lauroxil (AL) Komparator: paliperidone palmitate (156 mg and 234 mg monthly) or Placebo Endpunkt: changes in PANSS total score from baseline at approximately 12 weeks were of interest, weight gain of more than 7%, akathisia (i.e., sensation of rest- lessness and a sense of need for continuous motion), and treatment-emergent, nonakathisia, extrapyramidal symptom (EPS)- related adverse events (AEs) and treatment-emergent adverse events (TEAEs; e.g., pain at injection site, myalgia, dizziness, insomnia, headache, anxiety, agitation, nausea, vomiting, constipation, and suicidal ideation) were reviewed. Suchzeitraum (Aktualität der Recherche): November 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 RCTs (N=1589) Qualitätsbewertung der Studien: risk of bias Cochrane Handbook
	3. Ergebnisdarstellung <u>Eingeschlossenen Studien:</u> The four included studies enrolled a total of 1589 patients (400 for all AL doses, 576 for the PP doses used in this comparison, and 613 for the combined placebo groups). <u>Qualitätsbewertung:</u> high risk of bias for double blinding and allocation concealment for the study by Nasrallah et al. [21]. Attrition was high but similar in all four studies.

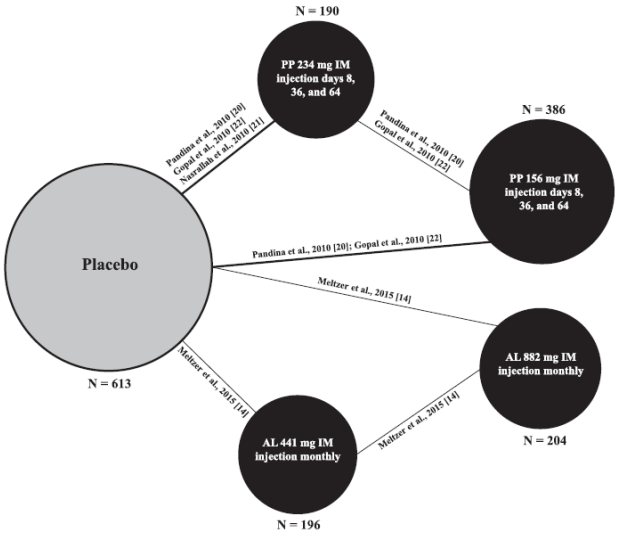


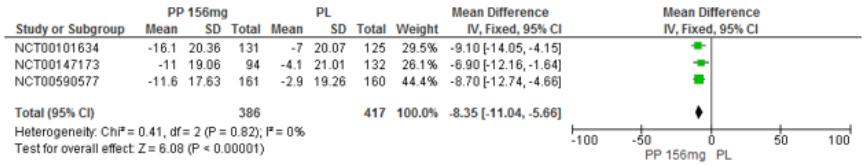
Fig. 1 – Evidence network for eligible randomized controlled trials. *Note.* Treatment nodes are sized to reflect the proportionate number of patients randomized to each treatment in the network. All pairwise comparisons were based on single studies. AL, aripiprazole lauroxil; IM, intramuscular; PP, paliperidone palmitate.

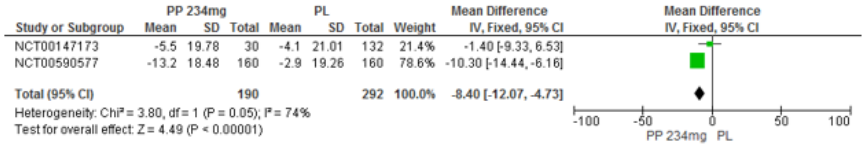
pairwise meta-analyses

Appendix 9 – Paliperidone palmitate pairwise meta-analysis for PANSS, TEAEs, and weight gain >7%

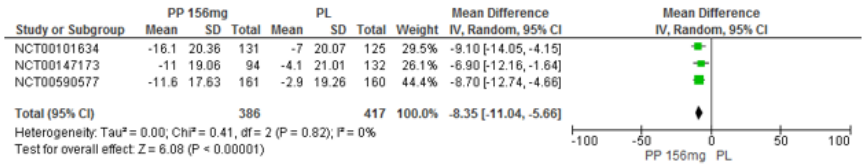
PANSS

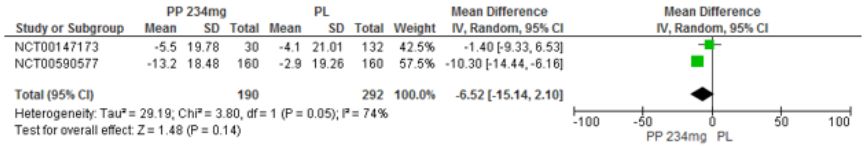
FE Model





RE Model



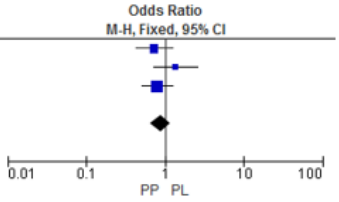


TEAEs

FE Model

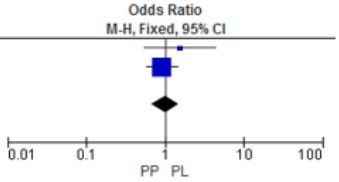
Study or Subgroup	PP 156mg Events	PP 156mg Total	PL Events	PL Total	Weight	Odds Ratio M-H, Fixed, 95% CI
NCT00101634	86	131	92	127	35.3%	0.73 [0.43, 1.24]
NCT00147173	79	97	103	135	17.6%	1.36 [0.71, 2.61]
NCT00590577	99	165	107	164	47.2%	0.80 [0.51, 1.25]
Total (95% CI)		**393**		**426**	**100.0%**	**0.87 [0.65, 1.18]**
Total events	264		302			

Heterogeneity: Chi² = 2.43, df = 2 (P = 0.30); I² = 18%
Test for overall effect: Z = 0.89 (P = 0.37)



Study or Subgroup	PP 234mg Events	PP 234mg Total	PL Events	PL Total	Weight	Odds Ratio M-H, Fixed, 95% CI
NCT00147173	25	30	103	135	13.7%	1.55 [0.55, 4.39]
NCT00590577	103	163	107	164	86.3%	0.91 [0.58, 1.44]
Total (95% CI)		**193**		**299**	**100.0%**	**1.00 [0.66, 1.51]**
Total events	128		210			

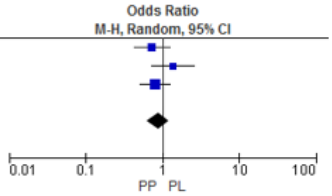
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)



RE Model

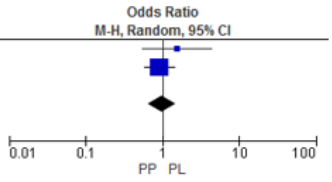
Study or Subgroup	PP 156mg Events	PP 156mg Total	PL Events	PL Total	Weight	Odds Ratio M-H, Random, 95% CI
NCT00101634	86	131	92	127	33.1%	0.73 [0.43, 1.24]
NCT00147173	79	97	103	135	23.6%	1.36 [0.71, 2.61]
NCT00590577	99	165	107	164	43.3%	0.80 [0.51, 1.25]
Total (95% CI)		**393**		**426**	**100.0%**	**0.88 [0.63, 1.23]**
Total events	264		302			

Heterogeneity: Tau² = 0.02; Chi² = 2.43, df = 2 (P = 0.30); I² = 18%
Test for overall effect: Z = 0.75 (P = 0.45)



Study or Subgroup	PP 234mg Events	PP 234mg Total	PL Events	PL Total	Weight	Odds Ratio M-H, Random, 95% CI
NCT00147173	25	30	103	135	15.9%	1.55 [0.55, 4.39]
NCT00590577	103	163	107	164	84.1%	0.91 [0.58, 1.44]
Total (95% CI)		**193**		**299**	**100.0%**	**1.00 [0.66, 1.51]**
Total events	128		210			

Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)

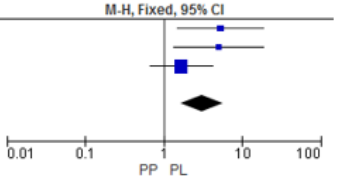


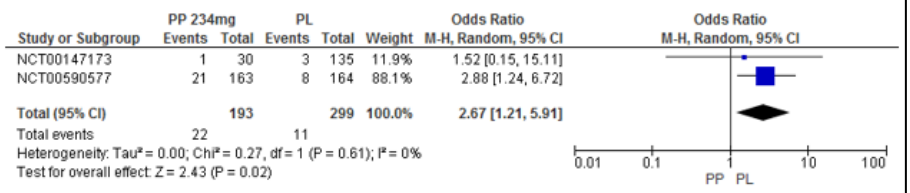
Weight Gain >7%

FE Model

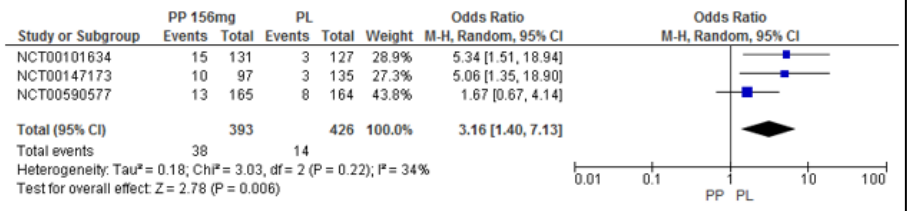
Study or Subgroup	PP 156mg Events	PP 156mg Total	PL Events	PL Total	Weight	Odds Ratio M-H, Fixed, 95% CI
NCT00101634	15	131	3	127	21.9%	5.34 [1.51, 18.94]
NCT00147173	10	97	3	135	18.2%	5.06 [1.35, 18.90]
NCT00590577	13	165	8	164	59.9%	1.67 [0.67, 4.14]
Total (95% CI)		**393**		**426**	**100.0%**	**3.09 [1.65, 5.78]**
Total events	38		14			

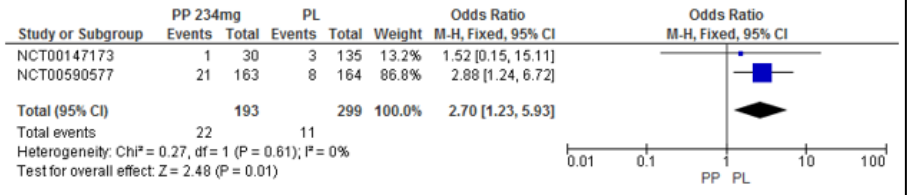
Heterogeneity: Chi² = 3.03, df = 2 (P = 0.22); I² = 34%
Test for overall effect: Z = 3.53 (P = 0.0004)





RE Model





CI = confidence interval; df = degrees of freedom; FE = fixed effects; IV = inverse variance; M-H = Mantel-Haenszel; PANSS = Positive and Negative Syndrome Scale; PL = placebo; PP = paliperidone palmitate; RE = random effects; SD = standard deviation; TEAE = treatment-emergent adverse event.

NMA

All four regimens were associated with reductions in PANSS total score compared with placebo and were of similar magnitude (range of mean differences –8.12 to g 95% CrIs).

The sensitivity analysis conducted to examine the impact of inclusion of the phase II PP study [18] on change in PANSS total score revealed only minor changes in the summary estimates for all comparisons

Corresponding values for p[best] and SUCRA were both lowest for placebo (p[best] = 0%, SUCRA = 0%), and values for both were highest for AL 882 mg (p[best] =55.6%, SUCRA = 83.7%). The findings remained the same for placebo in the adjusted analysis, and those for AL 882 mg decreased slightly (p[best] =50.4%, SUCRA = 80.1%) but remained the most favorable of the four active-treatment arms.

Weight gain

Comparisons of each active regimen versus placebo were asso- ciated with ORs of 1.74, 1.55, 3.47, and 3.14 for AL 441 mg, AL 882 mg, PP 156 mg, and PP 234 mg, respectively, with 95% CrIs for PP 156 mg and 234 mg excluding the null value of 1. No differences between active treatments were observed

Treatment-emergent adverse events

no differences for the comparisons between each active treatment and placebo. Similarly, there were no differences between the active treatments.

Extrapyramidal symptoms

no differences between the active treat- ments and placebo. Similarly, there were no differences between the active treatments.

	Akathisia Comparisons of each active regimen versus placebo suggested increases in the risk of akathisia with AL (OR 2.96 and 2.95 for the 441-mg and 882-mg doses, respectively; 95% CrIs excluded the null value of 1, meaning that subjects in both AL arms were more likely to have an akathisia AE compared with subjects receiving placebo). For PP, the comparison CrIs with placebo were not associated with increases (OR 0.99 and 1.14 for the 156-mg and 234-mg doses, respectively, with 95% CrIs that included the null value of 1). In comparisons between regimens, there were no differences between the AL and PP doses.
	4. Anmerkungen/Fazit der Autoren Our indirect comparison found no differences in total PANSS scores between AL and PP. Findings were consistent between the unadjusted analysis and adjusted analysis, in which we accounted for the slightly higher baseline PANSS total score in Meltzer et al. [14]. In general, the overall safety profiles for AL and PP were similar to those observed for oral forms. We found that AL was associated with an increase in akathisia relative to placebo, a finding consistent with the known safety profile of antipsychotic medications. Nevertheless, there were no differences between AL and PP. Furthermore, when akathisia was reported in Meltzer et al. [14], it tended to occur early in treatment and was generally mild to moderate in severity, unrelated to dose, and rarely resulted in treatment discontinuation. Similarly, consistent with observations among oral antipsychotic treatments, PP was associated with a greater risk of weight gain compared with placebo. We found no differences in TEAEs and treatment-emergent, nonakathisia, EPS-related AEs. The present NMA suggests that AL is associated with similar reductions in PANSS total score compared with PP in patients with schizophrenia experiencing an acute exacerbation. No differences in TEAEs, EPS, akathisia, or weight gain were found between AL and PP. These results suggest that clinicians can consider either AL or PP when treating adults experiencing an acute exacerbation of schizophrenia.
Zhu Y et al., 2017 [29]. Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses	1. Fragestellung The first episode of schizophrenia is a pivotal phase of this debilitating illness. Which drug to use remains controversial without a summary of all direct or indirect comparisons of drugs. We did a systematic review with pairwise and network meta-analyses of efficacy and tolerability.
	2. Methodik Population: first episode of schizophrenia or related disorders (eg, schizophreniform or schizoaffective disorders) → We accepted studies in which less than 20% of participants had psychiatric disorders other than schizophrenia (eg, depression or mental retardation) or less than 20% of participants were not having a first episode → flexible-dose studies Intervention/ Komparator: amisulpride, aripiprazole, asenapine, benperidol, brexpiprazole, cariprazine, chlorpromazine, clozapine, flupenthixol, fluphenazine, fluspirilene, haloperidol, iloperidone, levomepromazine, loxapine, lurasidone, molindone, olanzapine, paliperidone, quetiapine, penfluridol, perazine, perphenazine, pimozide, risperidone, sertindole, sulpiride, thioridazine, tiotixene, trifluoperazine, ziprasidone, zotepine, and zuclopenthixol (also known as clopenthixol). Endpunkt: overall change in symptoms of schizophrenia as measured by rating scales, such as the PANSS,23 the BPRS,24 or any other validated scale (eg,

	the Manchester Scale25); response (as defined in the study; if available, we preferred 50% reduction in PANSS or BPRS and Clinical Global Impression of at least much improved to lower thresholds26), change in positive symptoms of schizophrenia, change in negative symptoms of schizophrenia, study dropout for any reason (all-cause discontinuation), dropout because of inefficacy of treatment, use of drugs to treat parkinsonian symptoms, akathisia, weight gain (we extracted data on mean weight gain and weight gain for at least 7%, although in this study we analyse only mean change), increased prolactin release (we extracted data on mean change and number of participants with substantial increases, but analyse only mean change here), sedation, overall functioning, and quality of life. Suchzeitraum (Aktualität der Recherche): Nov. 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 19 RCTs (N=2669) Qualitätsbewertung: Cochrane risk of bias tool
	3. Ergebnisdarstellung *Fokus nur auf zugelassene Arzneimittel* *Qualitätsbewertung:* overall risk of bias findings are shown in the appendix (pp 23–25). Few details were reported about randomisation procedures and concealment of treatment allocation. 12 (63%) studies were double blind, three (16%) were single blind (those assessing outcomes were blinded), and four (21%) studies were open label. We judged five (26%) and two (11%) of the studies to have a high risk of bias in terms of attrition and selective reporting, respectively, and that only a few other studies had clear methodological problems, such as imbalance of groups at baseline. Nine (47%) studies were funded by pharmaceutical companies. The reports were published between 1987 and 2015, and provided comparisons of 12 antipsychotic drugs that were included in the network meta-analysis. 11 studies were of haloperidol, 13 of risperidone, seven of olanzapine, four of quetiapine, and one each of ziprasidone, zuclopenthixol, molindone, flupenthixol, pimozide, aripiprazole, amisulpride, and sertindole.

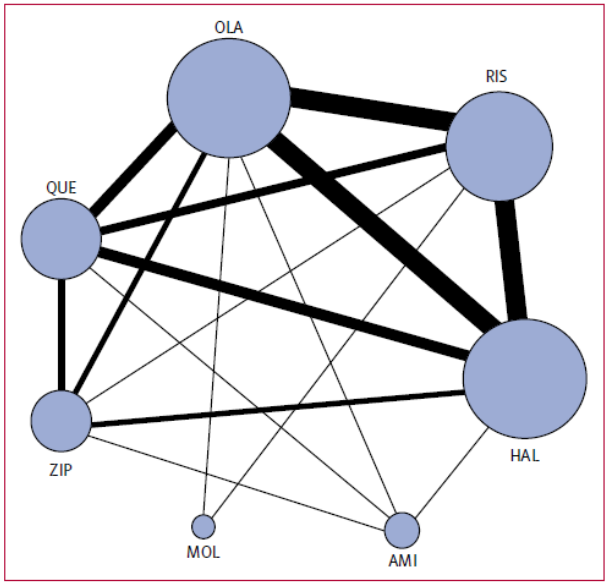


Figure 2: **Network plot of eligible comparisons for overall change in symptoms**
The circles (nodes) represent the available treatments and the lines (edges) represent the available comparisons. Sizes of nodes and width of edges indicate weighting according to the number of studies involved for each treatment and comparison, respectively. OLA=olanzapine. RIS=risperidone. HAL=haloperidol. AMI=amisulpride. MOL=molindone. ZIP=ziprasidone. QUE=quetiapine.

- We identified 19 relevant randomised controlled trials of 12 antipsychotic drugs that involved 2669 participants. 13 of the studies presented data on the primary outcome.
- For overall reduction of symptoms, amisulpride (SMD –0·37, 95% CI –0·61 to –0·14), olanzapine (–0·25, –0·39 to –0·12), ziprasidone (–0·25, –0·48 to –0·01), and risperidone (–0·14, –0·27 to –0·01) were significantly more efficacious than haloperidol, but the evidence was very low to moderate quality.
- Olanzapine was associated with less frequent use of drugs to treat parkinsonian symptoms than haloperidol, zuclopenthixol, and risperidone, and quetiapine was associated with less use of drugs to treat parkinsonian symptoms than haloperidol and zuclopenthixol.
- Quetiapine was associated with less akathisia than haloperidol, aripiprazole, risperidone, and olanzapine, and olanzapine with less than haloperidol, aripiprazole, and risperidone
- no significant differences between treatments for change in positive symptoms, but for change in negative symptoms, olanzapine was significantly more efficacious than haloperidol and risperidone
- Amisulpride was superior for reduction of symptoms to quetiapine (SMD –0·25, 95% CI –0·50 to –0·01). Olanzapine was superior to haloperidol and risperidone for reduction of negative symptoms. Several second-generation antipsychotics were superior to haloperidol in terms of all-cause discontinuation. Olanzapine was associated with at least one use of drugs to treat parkinsonian symptoms and quetiapine with less akathisia than haloperidol, aripiprazole, risperidone, and olanzapine, but, again, evidence was very low to low quality.
- Overall functioning and quality of life outcomes did not differ between drugs in pairwise meta-analyses, but very few data were available. No estimate was produced by network meta-analyses.
- When we excluded open-label studies from the sensitivity analysis for the primary outcome, olanzapine was superior to haloperidol and

quetiapine in the network meta-analysis.

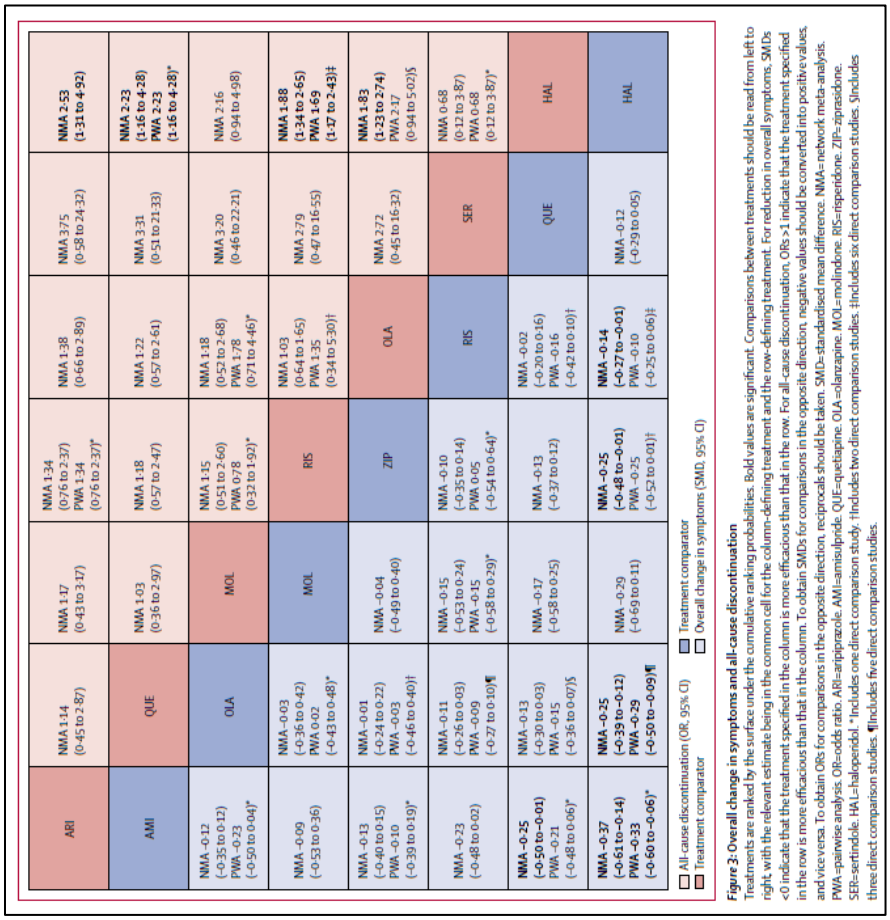


Figure 3: **Overall change in symptoms and all-cause discontinuation**
Treatments are ranked by the surface under the cumulative ranking probabilities. Bold values are significant. Comparisons between treatments should be read from left to right, with the relevant estimate being in the common cell for the column-defining treatment and the row-defining treatment. For reduction in overall symptoms, SMDs <0 indicate that the treatment specified in the column is more efficacious than that in the row. For all-cause discontinuation, ORs >1 indicate that the treatment specified in the row is more efficacious than that in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. SMD=standardised mean difference. NMA=network meta-analysis. PWA=pairwise analysis. OR=odds ratio. ARI=aripiprazole. AMI=amisulpride. QUE=quetiapine. OLA=olanzapine. MOL=molindone. RIS=risperidone. ZIP=ziprasidone. SER=sertindole. HAL=haloperidol. *Includes one direct comparison study. †Includes two direct comparison studies. ‡Includes six direct comparison studies. §Includes three direct comparison studies. ¶Includes five direct comparison studies.

4. Anmerkungen/Fazit der Autoren

Haloperidol seems to be a suboptimum treatment option for acute treatment of first-episode schizophrenia, but we found little difference between second-generation antipsychotics. The evidence was generally of low quality and the numbers of patients for each drug were small. Thus, the choice of treatment should be guided primarily by side-effects.

Leitlinien

Remington G et al., 2017 [22]. Guidelines for the Pharmacotherapy of Schizophrenia in Adults Siehe auch: **Norman R et al., 2017 [20].** Canadian Treatment Guidelines on Psychosocial Treatment of Schizophrenia in Adults	Fragestellung/Zielsetzung: The present guidelines address the pharmacotherapy of schizophrenia in adults across different stages, phases, and symptom domains. Canadian Health Care System Es handelt sich um eine Adaption von Leitlinien
	Methodik Grundlage der Leitlinie: • Guidelines were developed using the ADAPTE process, which takes advantage of existing guidelines. - national multidisciplinary panel Canada - identifying specific health questions; searching for and retrieving guidelines; assessing guideline quality, currency, content, consistency, and applicability; decision making around adaptation; and preparing the draft adapted guideline. - Recherche: systematisch in Medline und zielgerichtet auf Homepage der Organisationen - Identifizierten 6 Guidelines → evaluiert mit AGREE II - After reviewing the recommendations from the guidelines, the working groups decided which recommendations to accept and which to reject and which recommendations were acceptable but needed to be modified. - provided recommendations addressing the situation or topic. When de novo recommendations were created, the SIGN methodology was followed for the levels of evidence and the grades of recommendation - Each working group developed a final list of recommendations from the included guidelines - Recommendations required agreement by 80% of the group to be included in the Canadian guidelines. If a recommendation did not receive 80% agreement, the group discussed the recommendation and whether minor modifications to the recommendation would alter the likelihood that the recommendation would pass. In these situations, recommendations were modified (as described above) and the group revoted at a later date using an online anonymous survey. - The strength or grade of the recommendation is provided in brackets if applicable, using the system from which the recommendation came. • For those specific to the pharmacotherapy of schizophrenia in adults, a working group selected between guidelines and recommendations to create an adapted guideline. • Canadian Schizophrenia Guidelines were externally reviewed by those who will be affected by its uptake: practitioners, policy makers, health administrators, and patients and their families. LoE/ GoR:

Table 2. Grade/strength of recommendation classification systems for included guidelines.[a]

National Institute for Health and Care Excellence (NICE)

Strength of recommendations
The wording used denotes the certainty with which the recommendation is made (the strength of the recommendation).
Interventions that must (or must not) be used
We usually use "must" or "must not" only if there is a legal duty to apply the recommendation. Occasionally, we use "must" (or "must not") if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
Interventions that should (or should not) be used: a "strong" recommendation
We use "offer" (and similar words such as "refer" or "advise") when we are confident that, for the vast majority of patients, an intervention will do more good than harm and be cost-effective.
Interventions that could be used
We use "consider" when we are confident that an intervention will do more good than harm for most patients, and be cost-effective, but other options may be similarly cost-effective. The choice of an intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation.

Scottish Intercollegiate Guidelines Network (SIGN) and European Psychiatric Association

Levels of evidence
1++: High-quality meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a very low risk of bias; 1+: Well-conducted meta-analyses, systematic reviews, or randomized controlled trials with a low risk of bias; 1: Meta-analyses, systematic reviews, or randomized controlled trials with a high risk of bias
2++: High-quality systematic reviews of case control or cohort studies or high-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal; 2+: Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal; 2: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3: Nonanalytic studies (eg, case reports, case series)
4: Expert opinion
Grades of recommendation
A: At least one meta-analysis, systematic review, or randomized controlled trial rated as 1++ and directly applicable to the target population *or* a body of evidence consisting principally of studies rated as 1+, being directly applicable to the target population, and demonstrating overall consistency of results
B: A body of evidence including studies rated as 2++, being directly applicable to the target population, and demonstrating overall consistency of results *or* extrapolated evidence from studies rated as 1++ or 1+
C: A body of evidence including studies rated as 2+, being directly applicable to the target population, and demonstrating overall consistency of results *or* extrapolated evidence from studies rated as 2++
D: Evidence level 3 or 4 *or* extrapolated evidence from studies rated as 2+
Good Practice Point: Recommended best practice based on the clinical experience of the guideline's development group

American Psychiatric Association

Rating the strength of supporting research evidence
High (denoted by the letter *A*) = High confidence that the evidence reflects the true effect
Moderate (denoted by the letter *B*) = Moderate confidence that the evidence reflects the true effect
Low (denoted by the letter *C*) = Low confidence that the evidence reflects the true effect
Rating the strength of recommendations
Each guideline statement is separately rated to indicate the strength of the recommendation and the strength of supporting research evidence. "Strength of recommendation" describes the level of confidence that potential benefits of an intervention outweigh potential harms. This level of confidence is informed by available evidence, which includes evidence from clinical trials as well as expert opinion and patient values and preferences. The rating is a consensus judgment of the authors of the guideline and is endorsed by the Board of Trustees.
There are 2 possible ratings: recommendation or suggestion. "Recommendation" indicates confidence that the benefits of the intervention clearly outweigh harms. "Suggestion" indicates uncertainty (i.e., the balance of benefits and harms is difficult to judge or either the benefits or the harms are unclear).

[a]This is a condensed table; please see the Introduction and Methodology paper for full details.

Freitext/Empfehlungen/Hinweise

Eingeschlossene LL (Remington G et al., 2017):

Table 1. Clinical Practice Guidelines Used for the Canadian Schizophrenia Guidelines.

Guideline Developer	Guideline Title	Year Published
National Collaborating Centre for Mental Health Commissioned by the National Institute for Health and Care Excellence (NICE)	NICE National Clinical Guideline Number 178. Psychosis and Schizophrenia in Adults. Treatment and Management[3]	2014
National Collaborating Centre for Mental Health Commissioned by the National Institute for Health and Care Excellence (NICE)	NICE National Clinical Guideline Number 155. Psychosis and Schizophrenia in Children and Young People. Recognition and Management[4]	2013
National Collaborating Centre for Mental Health Commissioned by the National Institute for Health and Care Excellence	NICE National Clinical Guideline Number 120. Psychosis with Coexisting Substance Misuse. Assessment and Management in Adults and Young People[5]	2011
Scottish Intercollegiate Guidelines Network (SIGN)	SIGN 131. Management of Schizophrenia[6]	2013
European Psychiatric Association	European Psychiatric Association Guidance on the Early Intervention in Clinical High Risk States of Psychoses[7]	2015
American Psychiatric Association	American Psychiatric Association Practice Guidelines for Psychiatric Assessment of Adults[8]	2016

Recommendations: Pharmacotherapy of Schizophrenia in Adults

A. First-Episode Schizophrenia

Recommendation 1: Use of Antipsychotics

For patients with first-episode psychosis, antipsychotic medication should be recommended. [Modified from NICE (Strong recommendation)]

Recommendation 2: Antipsychotic Choice

Choice of antipsychotic medication should be made by the patient and

physician together, taking into account views of a carer where appropriate. Provide information and discuss the likely benefits and side effects of each drug. [NICE (Strong recommendation)]

- The inconsistency of findings argues against established clinical superiority for a specific antipsychotic in first-episode schizophrenia or, in fact, antipsychotic class (i.e., secondgeneration antipsychotic [SGA] vs. first-generation antipsychotic [FGA

18. Crossley NA, Constante M, McGuire P, et al. Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis. Br J Psychiatry. 2010;196(6): 434-439.

19. Zhang JP, Gallego JA, Robinson DG, et al. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and

meta-analysis. Int J Neuropsychopharmacol. 2013;16(6): 1205-1218.

20. Chatterjee A, Chakos M, Koreen A, et al. Prevalence and clinical correlates of extrapyramidal signs and spontaneous dyskinesia in never-medicated schizophrenic patients. Am J Psychiatry. 1995;152(12):1724-1729.

21. Zipursky RB, Gu H, Green AI, et al. Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. Br J Psychiatry. 2005;187(6): 537-543.

22. Emsley R, Rabinowitz J, Medori R. Remission in early psychosis: rates, predictors, and clinical and functional outcome correlates. Schizophr Res. 2007;89(1-3):129-139.

23. Green AI, Lieberman JA, Hamer RM, et al. Olanzapine and haloperidol in first episode psychosis: two-year data. Schizophr Res. 2006;86(1-3):234-243.

24. Robinson DG, Gallego JA, John M, et al. A randomized comparison of aripiprazole and risperidone for the acute treatment of first-episode schizophrenia and related disorders:

3-month outcomes. Schizophr Bull. 2015;41(6): 1227-1236.

Recommendation 3: Acute Antipsychotic Treatment

Following initiation of an antipsychotic medication for patients in the first episode of psychosis, the medication should be continued for at least 2 weeks unless there are significant tolerability issues. Assessment of dose and response should be monitored during the early phase of prescribing. Where there is poor response to medication, there should be assessment of medication adherence and substance use before lack of response can definitely be established. If there is no response to medication after 4 weeks, despite dose optimization, a change in antipsychotic should be considered. Where there is partial response, this should be reassessed after 8 weeks unless there are significant adverse events. [SIGN (Grade D)]

- This said, treatment must be individualized to accommodate tolerability and trajectory of response, both of which can vary between individuals.[27,28] In addition, it is essential to take into account nonpharmacological factors that can compromise response, in particular antipsychotic nonadherence and/or comorbid substance abuse.[29] Evidence indicates that clinicians' capacity to accurately identify those who are nonadherent is limited,[30,31]

27. Al-Dhaher Z, Kapoor S, Saito E, et al. Activating and tranquilizing effects of first-time treatment with aripiprazole, olanzapine, quetiapine, and risperidone in youth. J Child Adolesc

Psychopharmacol. 2016;26(5):458-470.

28. Levine SZ, Rabinowitz J. Trajectories and antecedents of treatment response over time in early-episode psychosis. Schizophr Bull. 2010;36(3):624-632.

29. Velligan DI, Weiden PJ, Sajatovic M, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009; 70(Suppl 4):1-46.

30. Acosta FJ, Bosch E, Sarmiento G, et al. Evaluation of noncompliance in schizophrenia patients using electronic monitoring (MEMS) and its relationship to sociodemographic, clinical and psychopathological variables. Schizophr Res. 2009;107(2-3): 213-217.

31. Remington G, Kwon J, Collins A, et al. The use of electronic monitoring (MEMS) to evaluate antipsychotic compliance in outpatients with schizophrenia. Schizophr Res. 2007;90(1-3): 229-237.

	Recommendation 4: Antipsychotic Dose and Trial Duration Target the lower end of the therapeutic effective dose range of antipsychotics to be used in individuals in the first episode of schizophrenia and titrate according to efficacy and tolerability. [Modified from SIGN (Grade D)] **Recommendation 5: Antipsychotic Continuation** Following resolution of positive symptoms of the first episode of schizophrenia, the duration of maintenance treatment with antipsychotics should be at least 18 months. [Modified from SIGN (Grade D)] *B. Acute Exacerbation* **Recommendation 1** Following an increase or change of antipsychotic medication in response to acute exacerbation of schizophrenia, the 608 The Canadian Journal of Psychiatry 62(9) medication should be continued for at least 4 weeks unless there are significant tolerability issues. Where a partial response is seen after review at 4 weeks, the medication should be reassessed after 8 weeks unless there are significant adverse effects. [Modified from SIGN (Grade D)] *C. Relapse Prevention and Maintenance Treatment* **Recommendation 1: Antipsychotic Dose** Following an acute episode of schizophrenia, individuals should be offered maintenance treatment with antipsychotic medication at low or moderate regular dosing of around 300 to 400 mg of chlorpromazine equivalents, 4 to 6 mg of risperidone, or other equivalents daily. [Modified from SIGN (Grade B)] **Recommendation 2: Duration of Treatment** Following resolution of positive symptoms of an acute episode of schizophrenia, patients should be offered maintenance treatment and antipsychotic medication for 2 and possibly up to 5 years or longer. [Modified from SIGN (Grade A)] **Recommendation 3: Antipsychotic Delivery** Patients should be given the option of oral or depot antipsychotic in line with their preference. [SIGN (Good Practice Point)] *D. Treatment-Resistant Schizophrenia (TRS)* **Recommendation 1: Clozapine** Clozapine should be offered to patients who have TRS. [SIGN (Grade A)] **Recommendation 2** Clozapine should be considered for patients whose schizophrenia has not responded to two antipsychotics. [Modified from SIGN (Grade B)] *E. Clozapine-Resistant Schizophrenia* **Recommendation 1: Definition of Clozapine-Resistan Schizophrenia** An adequate antipsychotic medication trial is defined as including the following: For oral antipsychotic drugs, at least 6 weeks of treatment at the midpoint or greater of the licensed therapeutic dose range. For LAI antipsychotic drugs, at least 6 weeks of treatment following reaching steady state (according to product monograph). For clozapine, at least 8 but preferably 12 weeks at a dose of 400 mg/d is an adequate trial; where available, obtaining trough levels 350 ng/mL (1100 nM/ L) for once-a-day dosing and 250 ng/mL for equal divided dosing is suggested. Documentation of adherence using approaches such as pill counts or dispensing chart reviews and, where available, with antipsychotic plasma levels on at least 1 occasion. Persistence of 2 or more positive symptoms with at least a

	moderate level of severity, or a single positive symptom with severe or greater severity, following 2 or more adequate trials with different antipsychotic drugs defines antipsychotic treatment–resistant Schizophrenia. Following an adequate trial with clozapine, if the criteria above continue to be met, the specifier clozapine-resistant schizophrenia should be added. **Recommendation 2** Treatment resistance in schizophrenia is a significant clinical concern and is associated with ongoing disability. The neurobiology of TRS shares some features with treatmentresponsive forms of the illness and has other distinct features. Defining antipsychotic treatment requires a strategy for assessing patient symptoms and assessing the adequacy of treatment. There is considerable variability in how treatment resistance is defined,80 and although the range of symptoms to be included in a definition of treatment resistance continues to be debated, positive symptoms are central. The assessment of response to antipsychotic medications or other treatments receives little attention in practice guidelines yet is critical for clinical decision making, especially regarding clozapine. The Health Canada approved monograph for Clozaril contains only 1 sentence of guidance: “Non-responsiveness is defined as the lack of satisfactory clinical response, despite treatment with appropriate courses of at least two marketed chemically-unrelated antipsychotic drugs.”81[De Novo Recommendation (Good Practice Point)] **Recommendation 3: Treatment Options** No recommendation. *Specific Symptom Domains* **Recommendation 1: Aggression and Hostility** The choice of medication for treatment of irritability, hostility, and aggression should be based on patient preference, past experience of antipsychotic treatment, the adverse effect profile, and concurrent medical history. For individuals with TRS accompanied by aggression/hostility, a trial of clozapine is indicated. [SIGN (Grade D)] **Recommendation 2: Comorbid Depressive Symptoms** Individuals who meet criteria for depressive disorder should be treated according to relevant clinical practice guidelines for depression, including the use of antidepressants. [SIGN (Good Practice Point)] **Eingeschlossene LL (Norman R et al., 2017):**

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American Psychiatric Association	American Psychiatric Association Practice Guidelines for Psychiatric Assessment of Adults[9]	2016

Family Intervention

Recommendation 1

Family intervention should be offered to all individuals diagnosed with schizophrenia who are in close contact with or live with family members and should be considered a priority when there are persistent symptoms or a high risk of relapse. Ten sessions over a 3-month period should be considered the minimum effective dose. Family intervention should encompass:

- Communication skills
- Problem solving
- Psychoeducation [From SIGN 2013]

Supported Employment Programs

Recommendation 2

Offer supported employment programs to people with psychosis or schizophrenia who wish to find or return to work (strong recommendation). Consider other occupational or educational activities, including prevocational training for people who are unable to work or unsuccessful in finding employment.

Recommendation 3

Mental health services should work in partnership with local stakeholders, including those representing minority groups, to enable people with psychosis or schizophrenia to stay in work or education and to assess new employment (including self-employment), volunteering, and educational activities [Modified from NICE (Strong)]

Cognitive-Behavioural Therapy

Recommendation 4

Cognitive-behavioural therapy (CBT) for psychosis should be offered to all

	individuals diagnosed with schizophrenia whose symptoms have not adequately responded to antipsychotic medication and are experiencing persisting symptoms, including anxiety or depression. CBT can be started during the initial phase, the acute phase, or recovery phase, including in-patient settings. [Modified from SIGN (Evidence level A)] **Recommendation 5** It is important that CBT be delivered by appropriately trained therapists following established, effective protocols, with regular supervision being available. It should be delivered in a collaborative manner and include established principles of CBT, including patients monitoring the relationship between their thoughts, feelings, behaviours, and symptoms; reevaluation of perceptions, beliefs, and thought processes that contribute to symptoms; promotion of beneficial ways of coping with symptoms; reduction of stress; and improvement of functioning. The minimum dose of CBT should be regarded as 16 sessions. [Modified from NICE (Strong)] *Cognitive Remediation* **Recommendation 6** Cognitive remediation therapy (CRT) may be considered for individuals diagnosed with schizophrenia who have persisting problems associated with cognitive difficulties. [From SIGN (Recommendation grade B)] *Social Skills Training* **Recommendation 7** Social skills training should be available for patients who are having difficulty and/or experiencing stress and anxiety related to social interaction. [De novo recommendation (Evidence grade B)] *Life Skills Training* **Recommendation 8** Life skills training should be available for patients who are having difficulty with self-care related to housekeeping, transportation, financial management, and so on. [De novo recommendation (Evidence level: Low)] *Patient Education* **Recommendation 9** Appropriate education for patients about the nature and treatment of and recovery from schizophrenia should be an integral part of a program of treatment, but education interventions in themselves do not have robust effects on treatment outcomes. [De novo recommendation (Evidence level: Low)]
NICE 2014, [18] Psychosis and Schizophrenia in adults Siehe auch: **NICE, 2014 [19].** Psychosis and schizophrenia in adults: prevention and management	Fragestellung/Zielsetzung: The guideline makes recommendations for the treatment and management of psychosis and schizophrenia. It aims to: - improve access and engagement with treatment and services for people with psychosis and schizophrenia - evaluate the role of specific psychological, psychosocial and pharmacological interventions in the treatment of psychosis and schizophrenia - evaluate the role of psychological and psychosocial interventions in combination with pharmacological interventions in the treatment of psychosis and schizophrenia - evaluate the role of specific service-level interventions for people with

	psychosis and schizophrenia - integrate the above to provide best-practice advice on the care of individuals throughout the course of their psychosis and schizophrenia - promote the implementation of best clinical practice through the development of recommendations tailored to the requirements of the NHS in England and Wales.
	Methodik Grundlage der Leitlinie The development of this guideline followed The Guidelines Manual (NICE, 2012b). A team of health care professionals, lay representatives and technical experts known as the Guideline Development Group (GDG), with support from the NCCMH staff, undertook the development of a person-centred, evidence-based guideline. There are seven basic steps in the process of developing a guideline: - 1. Define the scope, which lays out exactly what will be included (and excluded) in the guidance. - 2. Define review questions that cover all areas specified in the scope. - 3. Develop a review protocol for the systematic review, specifying the search strategy and method of evidence synthesis for each review question. - 4. Synthesise data retrieved, guided by the review protocols. - 5. Produce evidence profiles and summaries using the Grading of - Recommendations Assessment, Development and Evaluation (GRADE) approach. - 6. Consider the implications of the research findings for clinical practice and reach consensus decisions on areas where evidence is not found. - 7. Answer review questions with evidence-based recommendations for clinical practice. The clinical practice recommendations made by the GDG are therefore derived from the most up-to-date and robust evidence for the clinical and cost effectiveness of the interventions and services used in the treatment and management of people with psychosis and schizophrenia in adults. Where evidence was not found or was inconclusive, the GDG discussed and attempted to reach consensus on what should be recommended, factoring in any relevant issues. In addition, to ensure a service user and carer focus, the concerns of service users and carers regarding health and social care have been highlighted and addressed by recommendations agreed by the whole GDG. A GRADE evidence profile was used to summarise both the quality of the evidence and the results of the evidence synthesis for each ‘critical’ and ‘important’ outcome

Recommendations are marked as **[2009]**, **[2009, amended 2014]**, **[2014]** or **[new 2014]**.

- **[2009]** indicates that the evidence has not been reviewed since 2009.
- **[2009, amended 2014]** indicates that the evidence has not been reviewed since 2009 but changes have been made to the recommendation wording that change the meaning (see below).
- **[2014]** indicates that the evidence has been reviewed but no changes have been made to the recommendation.
- **[new 2014]** indicates that the evidence has been reviewed and the recommendation has been updated or added.

Recommendations from NICE clinical guideline 82 that have been amended

Recommendations are labelled **[2009, amended 2014]** if the evidence has not been reviewed since 2009 but changes have been made to the recommendation wording that change the meaning.

Recommendation in 2009 guideline	Recommendation in current guideline	Reason for change

Freitext/Empfehlungen/Hinweise

Hinweis: Summary of recommendations beziehen sich zVT-Kriterien

14.2 PREVENTING PSYCHOSIS

14.2.1 Referral from primary care

14.2.1.1 If a person is distressed, has a decline in social functioning and has:

- transient or attenuated psychotic symptoms or
- other experiences or behaviour suggestive of possible psychosis or
- a first-degree relative with psychosis or schizophrenia

refer them for assessment without delay to a specialist mental health service or an early intervention in psychosis service because they may be at increased risk of developing psychosis. [new 2014]

14.2.2 Specialist assessment

14.2.2.1 A consultant psychiatrist or a trained specialist with experience in at-risk mental states should carry out the assessment. [new 2014]

14.2.3 Treatment options to prevent psychosis

14.2.3.1 If a person is considered to be at increased risk of developing psychosis (as described in recommendation 14.2.1.1):

- offer individual cognitive behavioural therapy (CBT) with or without family intervention (delivered as described in recommendations 14.3.7.1 and 14.3.7.2) and • offer interventions recommended in NICE guidance for people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse. [new 2014]

14.2.3.2 Do not offer antipsychotic medication:

- to people considered to be at increased risk of developing psychosis (as described in recommendation 14.2.1.1) or
- with the aim of decreasing the risk of or preventing psychosis. [new 2014]

14.2.4 Monitoring and follow-up

14.2.4.1 If, after treatment (as described in recommendation 14.2.3.1), the person continues to have symptoms, impaired functioning or is distressed, but a clear diagnosis of psychosis cannot be made, monitor the person regularly for changes in symptoms and functioning for up to 3 years using a structured and validated assessment tool. Determine the frequency and duration of monitoring by the:

- severity and frequency of symptoms
- level of impairment and/or distress and
- degree of family disruption or concern. [new 2014]

14.2.4.2 If a person asks to be discharged from the service, offer follow-up appointments and the option to self-refer in the future. Ask the person's GP to continue monitoring changes in their mental state. [new 2014]

14.3FIRST EPISODE PSYCHOSIS

14.3.1Early intervention in psychosis services

14.3.1.1 Early intervention in psychosis services should be accessible to all people with a first episode or first presentation of psychosis, irrespective of the person's age or the duration of untreated psychosis. [new 2014]

14.3.1.2 People presenting to early intervention in psychosis services should be assessed without delay. If the service cannot provide urgent intervention for people in a crisis, refer the person to a crisis resolution and home treatment team (with support from early intervention in psychosis services). Referral may be from primary or secondary care (including other community services) or a self- or carer-referral. [new 2014]

14.3.1.3 Early intervention in psychosis services should aim to provide a full range of pharmacological, psychological, social, occupational and educational interventions for people with psychosis, consistent with this guideline. [2014]

14.3.1.4 Consider extending the availability of early intervention in psychosis services beyond 3 years if the person has not made a stable recovery from psychosis or schizophrenia. [new 2014]

14.3.2 Primary care

14.3.2.1 Do not start antipsychotic medication for a first presentation of sustained

psychotic symptoms in primary care unless it is done in consultation with a

consultant psychiatrist. [2009; amended 2014]

14.3.4Treatment options

14.3.4.1 For people with first episode psychosis offer:

- oral antipsychotic medication (see sections 14.3.5.and 14.3.6) in conjunction with
- psychological interventions (family intervention and individual CBT, delivered as described in recommendations 14.3.7.1 and 14.3.7.2). [new 2014]

14.3.4.2 Advise people who want to try psychological interventions alone that these are more effective when delivered in conjunction with antipsychotic medication. If the person still wants to try psychological interventions alone:

- offer family intervention and CBT
- agree a time (1 month or less) to review treatment options, including introducing antipsychotic medication

	- continue to monitor symptoms, distress, impairment and level of functioning (including education, training and employment) regularly. [new 2014] 14.3.4.3 If the person's symptoms and behaviour suggest an affective psychosis or disorder, including bipolar disorder and unipolar psychotic depression, follow the recommendations in Bipolar disorder (NICE clinical guideline 38) or Depression (NICE clinical guideline 90). [new 2014] **14.3.5Choice of antipsychotic medication** 14.3.5.1 The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Provide information and discuss the likely benefits and possible side effects of each drug, including: - metabolic (including weight gain and diabetes) - extrapyramidal (including akathisia, dyskinesia and dystonia) - cardiovascular (including prolonging the QT interval) - hormonal (including increasing plasma prolactin) - other (including unpleasant subjective experiences). [2009; amended 2014] **14.3.6How to use antipsychotic medication** 14.3.6.1 Before starting antipsychotic medication, undertake and record the following baseline investigations: - weight (plotted on a chart) - waist circumference - pulse and blood pressure - fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels - assessment of any movement disorders - assessment of nutritional status, diet and level of physical activity. [new 2014] 14.3.6.2 Before starting antipsychotic medication, offer the person with psychosis or schizophrenia an electrocardiogram (ECG) if: - specified in the summary of product characteristics (SPC) - a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure) - there is a personal history of cardiovascular disease or - the service user is being admitted as an inpatient. [2009] 14.3.6.3 Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. Include the following: - Discuss and record the side effects that the person is most willing to tolerate. - Record the indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects. - At the start of treatment give a dose at the lower end of the licensed range and slowly titrate upwards within the dose range given in the

	British national formulary (BNF) or SPC. - Justify and record reasons for dosages outside the range given in the BNF or SPC. - Record the rationale for continuing, changing or stopping medication, and the effects of such changes. - Carry out a trial of the medication at optimum dosage for 4–6 weeks. [2009; amended 2014] 14.3.6.4 Monitor and record the following regularly and systematically throughout treatment, but especially during titration: - response to treatment, including changes in symptoms and behaviour - side effects of treatment, taking into account overlap between certain side effects and clinical features of schizophrenia (for example, the overlap between akathisia and agitation or anxiety) and impact on functioning - the emergence of movement disorders - weight, weekly for the first 6 weeks, then at 12 weeks, at 1 year and then annually (plotted on a chart) - waist circumference annually (plotted on a chart) - pulse and blood pressure at 12 weeks, at 1 year and then annually - fasting blood glucose, HbA1c and blood lipid levels at 12 weeks, at 1 year and then annually - adherence - overall physical health. [new 2014] 14.3.6.5 The secondary care team should maintain responsibility for monitoring service users' physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements. [new 2014] 14.3.6.6 Discuss any non-prescribed therapies the service user wishes to use (including complementary therapies) with the service user, and carer if appropriate. Discuss the safety and efficacy of the therapies, and possible interference with the therapeutic effects of prescribed medication and psychological treatments. [2009] 14.3.6.7 Discuss the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs with the service user, and carer if appropriate. Discuss their possible interference with the therapeutic effects of prescribed medication and psychological treatments. [2009] 14.3.6.8 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 14.3.6.3. Review clinical indications, frequency of administration, therapeutic benefits and side effects each week or as appropriate. Check whether 'p.r.n.' prescriptions have led to a dosage above the maximum specified in the BNF or SPC. [2009] 14.3.6.9 Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation'). [2009] 14.3.6.10 Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication). [2009] 14.3.6.11 If prescribing chlorpromazine, warn of its potential to cause skin

	photosensitivity. Advise using sunscreen if necessary. [2009] **14.3.7How to deliver psychological interventions** 14.3.7.1 CBT should be delivered on a one-to-one basis over at least 16 planned session and: Follow a treatment manual so that: - people can establish links between their thoughts, feelings or actions and their current or past symptoms, and/or functioning - the re-evaluation of people's perceptions, beliefs or reasoning - relates to the target symptoms also include at least one of the following components: - people monitoring their own thoughts, feelings or behaviours with respect to their symptoms or recurrence of symptoms - promoting alternative ways of coping with the target symptom - reducing distress - improving functioning. [2009] 14.3.7.2 Family intervention should: - include the person with psychosis or schizophrenia if practical - be carried out for between 3 months and 1 year - include at least 10 planned sessions - take account of the whole family's preference for either singlefamily intervention or multi-family group intervention - take account of the relationship between the main carer and the person with psychosis or schizophrenia - have a specific supportive, educational or treatment function and include negotiated problem solving or crisis management work. [2009] **14.3.8 Monitoring and reviewing psychological interventions** 14.3.8.1 When providing psychological interventions, routinely and systematically monitor a range of outcomes across relevant areas, including service user satisfaction and, if appropriate, carer satisfaction. [2009] 14.3.8.2 Healthcare teams working with people with psychosis or schizophrenia should identify a lead healthcare professional within the team whose responsibility is to monitor and review: - access to and engagement with psychological interventions - decisions to offer psychological interventions and equality of access across different ethnic groups. [2009] **14.3.9 Competencies for delivering psychological interventions** 14.3.9.1 Healthcare professionals providing psychological interventions should: - have an appropriate level of competence in delivering the intervention to people with psychosis or schizophrenia - be regularly supervised during psychological therapy by a competent therapist and supervisor. [2009] 14.3.9.2 Trusts should provide access to training that equips healthcare professionals with the competencies required to deliver the psychological therapy interventions recommended in this guideline. [2009]

	14.4.2 Treatment options 14.4.2.1 For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer: - oral antipsychotic medication in conjunction (see sections 14.3.5. and 14.3.6 with - psychological interventions (family intervention and individual CBT, delivered as described in recommendations 14.3.7.1 and 14.3.7.2). [new 2014] **14.4.3 Pharmacological interventions** 14.4.3.1 For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication or review existing medication. The choice of drug should be influenced by the same criteria recommended for starting treatment (see sections 14.3.5.and 14.3.6). Take into account the clinical response and side effects of the service user's current and previous medication. [2009; amended 2014] **14.4.4 Psychological and psychosocial interventions** 14.4.4.1 Offer CBT to all people with psychosis or schizophrenia (delivered as described in recommendation 14.3.7.1). This can be started either during the acute phase or later, including in inpatient settings. [2009] 14.4.4.2 Offer family intervention to all families of people with psychosis or schizophrenia who live with or are in close contact with the service user (delivered as described in recommendation 14.3.7.2). This can be started either during the acute phase or later, including in inpatient settings. [2009] 14.4.4.3 Consider offering arts therapies to all people with psychosis or schizophrenia, particularly for the alleviation of negative symptoms. This can be started either during the acute phase or later, including in inpatient settings. [2009] 14.4.4.4 Arts therapies should be provided by a Health and Care Professions Council registered arts therapist with previous experience of working with people with psychosis or schizophrenia. The intervention should be provided in groups unless difficulties with acceptability and access and engagement indicate otherwise. Arts therapies should combine psychotherapeutic techniques with activity aimed at promoting creative expression, which is often unstructured and led by the service user. Aims of arts therapies should include: - enabling people with psychosis or schizophrenia to experience themselves differently and to develop new ways of relating to others - helping people to express themselves and to organise their experience into a satisfying aesthetic form - helping people to accept and understand feelings that may have emerged during the creative process (including, in some cases, how they came to have these feelings) at a pace suited to the person. [2009] 14.4.4.5 When psychological treatments, including arts therapies, are started in the acute phase (including in inpatient settings), the full course should be continued after discharge without unnecessary interruption. [2009] 14.4.4.6 Do not routinely offer counselling and supportive psychotherapy (as specific interventions) to people with psychosis or schizophrenia. However, take service user preferences into account, especially if other more efficacious psychological treatments, such as CBT, family intervention and arts therapies, are not available locally. [2009]

	14.4.4.7 Do not offer adherence therapy (as a specific intervention) to people with psychosis or schizophrenia. [2009] 14.4.4.8 Do not routinely offer social skills training (as a specific intervention) to people with psychosis or schizophrenia. [2009] **14.4.5 Behaviour that challenges** 14.4.5.1 Occasionally people with psychosis or schizophrenia pose an immediate risk to themselves or others during an acute episode and may need rapid tranquillisation. The management of immediate risk should follow the relevant NICE guidelines (see recommendations 14.4.5.2 and 14.4.5.5). [2009] 14.4.5.2 Follow the recommendations in Violence (NICE clinical guideline 25) when facing imminent violence or when considering rapid tranquillisation. [2009] 14.4.5.3 After rapid tranquillisation, offer the person with psychosis or schizophrenia the opportunity to discuss their experiences. Provide them with a clear explanation of the decision to use urgent sedation. Record this in their notes. [2009] 14.4.5.4 Ensure that the person with psychosis or schizophrenia has the opportunity to write an account of their experience of rapid tranquillisation in their notes. [2009] 14.4.5.5 Follow the recommendations in Self-harm (NICE clinical guideline 16) when managing acts of self-harm in people with psychosis or schizophrenia. [2009] <u>Relapse and re-referral to secondary care</u> 14.5.3.6 When a person with an established diagnosis of psychosis or schizophrenia presents with a suspected relapse (for example, with increased psychotic symptoms or a significant increase in the use of alcohol or other substances), primary healthcare professionals should refer to the crisis section of the care plan. Consider referral to the key clinician or care coordinator identified in the crisis plan. [2009] 14.5.3.7 For a person with psychosis or schizophrenia being cared for in primary care, consider referral to secondary care again if there is: - poor response to treatment - non-adherence to medication - intolerable side effects from medication - comorbid substance misuse - risk to self or others. [2009] 14.5.3.8 When re-referring people with psychosis or schizophrenia to mental health services, take account of service user and carer requests, especially for: - review of the side effects of existing treatments - psychological treatments or other interventions. [2009] <u>Transfer</u> 14.5.3.9 When a person with psychosis or schizophrenia is planning to move to the catchment area of a different NHS trust, a meeting should be arranged between the services involved and the service user to agree a transition plan before transfer. The person's current care plan should be sent to the new secondary care and primary care providers. [2009] **14.5.4 Psychological interventions**

	14.5.4.1 Offer CBT to assist in promoting recovery in people with persisting positive and negative symptoms and for people in remission. Deliver CBT as described in recommendation 14.3.7.1. [2009] 14.5.4.2 Offer family intervention to families of people with psychosis or schizophrenia who live with or are in close contact with the service user. Deliver family intervention as described in recommendation 14.3.7.2. [2009] 14.5.4.3 Family intervention may be particularly useful for families of people with psychosis or schizophrenia who have: - recently relapsed or are at risk of relapse - persisting symptoms. [2009] 14.5.4.4 Consider offering arts therapies to assist in promoting recovery, particularly in people with negative symptoms. [2009] **14.5.5 Pharmacological interventions** 14.5.5.1 The choice of drug should be influenced by the same criteria recommended for starting treatment (see sections 14.3.5.and 14.3.6). [2009] 14.5.5.2 Do not use targeted, intermittent dosage maintenance strategies60 routinely. However, consider them for people with psychosis or schizophrenia who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy, such as side-effect sensitivity. [2009] 14.5.5.3 Consider offering depot /long-acting injectable antipsychotic medication to people with psychosis or schizophrenia: - who would prefer such treatment after an acute episode - where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan. [2009] **14.5.6 Using depot/long-acting injectable antipsychotic medication** 14.5.6.1 When initiating depot/long-acting injectable antipsychotic medication: - take into account the service user's preferences and attitudes towards the mode of administration (regular intramuscular injections) and organisational procedures (for example, home visits and location of clinics) - take into account the same criteria recommended for the use of oral antipsychotic medication (see sections 14.3.5 and 14.3.6), particularly in relation to the risks and benefits of the drug regimen - initially use a small test dose as set out in the BNF or SPC. [2009] **14.5.7 Interventions for people whose illness has not responded adequately to treatment** 14.5.7.1 For people with schizophrenia whose illness has not responded adequatelyto pharmacological or psychological treatment: - Review the diagnosis. - Establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration. - Review engagement with and use of psychological treatments and ensure that these have been offered according to this guideline. If family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for people in close contact with their families.

	- Consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness. [2009] 14.5.7.2 Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs. At least 1 of the drugs should be a non-clozapine second-generation antipsychotic. [2009] 14.5.7.3 For people with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, healthcare professionals should consider recommendation 14.5.7.1(including measuring therapeutic drug levels) before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks. Choose a drug that does not compound the common side effects of clozapine. [2009]
Baandrup L et al., 2016 [1]. Treatment of adult patients with schizophrenia and complex mental health needs – A national clinical guideline	Fragestellung/Zielsetzung: The Danish Health and Medicines Authority assembled a group of experts to develop a national clinical guideline for patients with schizophrenia and complex mental health needs. The aim of this study was to develop an evidence-based national clinical guideline for the treatment of patients with schizophrenia and complex mental health needs. The guideline comprised the following 10 explicit review questions: Pharmacological treatment (1) What are the consequences of reducing the clozapine dosage in schizophrenia patients with satisfactory symptomatic improvement, but with plasma clozapine levels above the upper limit in the therapeutic range? (2) What is the effect of long-acting injectable antipsychotics in schizophrenia patients with poor medication adherence and persisting positive symptoms? (3) What is the effect of SSRI/SNRI add-on therapy to treat persistent negative symptoms in patients with schizophrenia? (4) What is the effect of discontinuing antipsychotic treatment in patients with schizophrenia and insufficient response to previous antipsychotic treatment (provided adequate dosing and duration of several antipsychotic compounds including clozapine)? Psychosocial and psychotherapeutic treatment (5) What is the effect of family intervention in patients with schizophrenia and functional impairment? (6) What is the effect of neurocognitive training in patients with schizophrenia and functional impairment? (7) What is the effect of social cognitive training in patients with schizophrenia and functional impairment? (8) What is the effect of cognitive behavioural therapy in patients with schizophrenia and functional impairment? (9) What is the effect of combining cognitive behavioural therapy and motivational interviewing in the treatment of schizophrenia patients with co-morbid cannabis and/or central stimulant abuse? Access and engagement (10) What is the effect of assertive community treatment (ACT) in schizophrenia patients with difficulties retaining contact with outpatient mental health care facilities?

	Methodik Grundlage der Leitlinie • Clinical guideline was developed according to the GRADE system • comprising professionals in psychiatry, clinical psychology, nursing, general practice, and academic experts in psychiatry and psychology • Zielformulierung nach PICO • Syst. Literature search was carried out from 3 July to 5 December 2014 • All relevant guidelines were evaluated using the Appraisal of Guidelines for Research and Evaluation Instrument (AGREE II) • Searching for systematic reviews and meta-analyses from the date where the relevant retrieved guideline(s) (if any) ended their literature search (AMSTAR) plus Cochrane Collaboration's tool for assessing risk of bias. • The GDG then formulated recommendations • for each intervention examined, taking into account the quality of the evidence, the balance between desirable and undesirable effects, and the perceived patient preference with regard to the intervention (1,5,6). In the absence of evidence, a group discussion and consensus process was adopted, and the GDG decided on a good practice recommendation. • Various stakeholders had the opportunity to comment on the draft guideline during a consultation period preceding the publication of the guideline. Following the consultation, all comments from the stakeholders and two specifically appointed expert peer-reviewers were discussed by the review team and the GDG, and the guideline was revised accordingly by the GDG. • Organizational and health economic issues were per definition not considered in the development of this national clinical guideline. LOE √ Good practice (in the absence of any relevant evidence). ↑↑ Strong recommendation for the experimental intervention. ↑ Weak recommendation for the experimental intervention. ↓ Weak recommendation against the experimental intervention.
	Freitext/Empfehlungen/Hinweise

Table 1. Summary of the clinical guideline recommendations.

Pharmacological treatment	
√	It is good practice to adjust clozapine dosage according to the clinical response and the individual tolerability, even if this implies exceeding the upper limit in the defined therapeutic range. However, clozapine levels above the upper limit in this range always indicate a need to reconsider whether the patient could be managed on a lower dosage.
√	For patients with no previous or current response to several antipsychotic compounds, including clozapine, it is good practice to gradually taper any on-going antipsychotic treatment, paying particular attention to the risk of aggravated psychotic symptoms.
↑↑	Maintenance antipsychotic treatment should be used routinely for non-remitted schizophrenia patients with a previous antipsychotic drug response.
↑	Long-acting injectable antipsychotics should be considered for the treatment of schizophrenia patients with poor medication adherence.
↓	SSRI/SNRI add-on therapy for persisting negative symptoms should be used only cautiously and after careful consideration.
Psychosocial and psychotherapeutic treatment	
↑↑	Family intervention should be offered routinely to schizophrenia patients with impaired functioning.
↑	Neurocognitive training should be considered for the treatment of schizophrenia patients with impaired functioning.
↑	Social cognitive training should be considered for the treatment of schizophrenia patients with impaired functioning.
↑	Cognitive behavioural therapy should be considered for the treatment of schizophrenia patients with persisting positive and/or negative symptoms.
↑	The combination of cognitive behavioural therapy and motivational interviewing should be considered for the treatment of schizophrenia patients with co-morbid cannabis and/or central stimulant abuse.
Access and engagement	
↑↑	Assertive community treatment should be used routinely for schizophrenia patients who cannot comply with usual outpatient mental health care settings.

√ Good practice (in the absence of any relevant evidence).
↑↑ Strong recommendation for the experimental intervention.
↑ Weak recommendation for the experimental intervention.
↓ Weak recommendation against the experimental intervention.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Hasan A et al., 2013 [10].

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 2: Update 2012
on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects

Category of Evidence		Description
A		**Full Evidence From Controlled Studies is based on:** Two or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo" in a study with adequate blinding) **and** One or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists) In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least two more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfil established methodological standards. The decision is based on the primary efficacy measure.
B		**Limited Positive Evidence From Controlled Studies is based on:** One or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") **or** a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial **and** no negative studies exist
C		**Evidence from Uncontrolled Studies or Case Reports/Expert Opinion**
	C1	**Uncontrolled Studies. Evidence is based on:** 1 or more positive naturalistic open studies (with a minimum of 5 evaluable patients) **or** a comparison with a reference drug with a sample size insufficient for a non-inferiority trial **and** no negative controlled studies exist
	C2	**Case Reports. Evidence is based on:** 1 or more positive case reports **and** no negative controlled studies exist
	C3	Evidence is based on the opinion of experts in the field or clinical experience
D		**Inconsistent Results** Positive RCTs are outweighed by an approximately equal number of negative studies
E		**Negative Evidence** The majority of RCTs studies or exploratory studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") or inferiority to comparator treatment
F		**Lack of Evidence** Adequate studies proving efficacy or non-efficacy are lacking.
Recommendation Grade		**Based on**
1		**Category A evidence and good risk-benefit ratio**
2		**Category A evidence and moderate risk-benefit ratio**
3		**Category B evidence**
4		**Category C evidence**
5		**Category D evidence**

Antipsychotic treatment

- Antipsychotics (FGAs and SGAs) are effective in relapse prevention and should be offered to a patient suffering from schizophrenia (Category of evidence A, Recommendation grade 1).
- FGAs and SGAs do not show general differences in reducing symptoms with long term treatment (Category of evidence A, Recommendation grade 1).
- Some evidence is available to support superiority of certain SGAs (as outlined in these guidelines) with regard to treatment discontinuation and relapse prevention (Category of Evidence B, Recommendation grade 3).
- The reduced risk of inducing motor side effects (especially tardive dyskinesia) might favour certain SGAs (Category of evidence C, Recommendation grade 4).
- In the long-term treatment, where the secondary negative symptoms become less prominent, certain SGAs may have some advantages in reducing negative symptoms (Category of evidence C, Recommendation grade 4).
- For long-term therapy, tardive dyskinesia and metabolic side effects seem to have the greatest impact on the patient ' s wellbeing and health – these side effects, among others (see Part 1 of these guidelines), need to be monitored continuously and treated as soon as

	possible (Category of evidence C, Recommendation grade 4). – The choice of the antipsychotic should be infl uenced by the same criteria recommended for starting a treatment (Good Clinical Practice). – Maintenance treatment should be carried forward with the antipsychotic drug which led to the best response and which had the best individual side effect profi le during the acute episode (Good Clinical Practice). – Each antipsychotic selection procedure must be undertaken individually, respecting the patient's experience with certain drug classes and the individual side effect profi le. **Duration of long-term treatment** – A continuous antipsychotic for at least one year for fi rst-episode patients is recommended (Category of evidence C, Recommendation grade 4) – For multiple-episode patients, maintenance treatment duration of at least 2 – 5 years (in severe cases life-long treatment) should be taken into consideration (Category of evidence C, Recommendation grade 4). – Nevertheless, the duration of treatment should be determined on an individual basis, taking into account the patient ' s motivation, the psychosocial situation and the additional care being given. Indefi nite continuation of antipsychotic medications is recommended for patients with a history of serious suicide attempts or violent, aggressive behaviour and very frequent relapses (Category of evidence C, Recommendation grade 4). **First-generation depot antipsychotics** – Currently, there is good evidence to support the use of FGA depot antipsychotics for relapse prevention in schizophrenia (Category of evidence A, Recommendation grade 1) , but no clear difference in effi cacy between oral and depot formulations can be stated (Category of evidence A, Recommendation grade 1) . – There is good evidence to support the use of long-acting injectable risperidone for the treatment of schizophrenia (Category of evidence A, Recommendation grade 1). – There is some evidence to support a superiority of the depot compared to the oral preparation (Category of evidence C, Recommendation grade 4). – There is some evidence for the use of longacting injectable risperidone in fi rst-episode schizophrenia patients and elderly patients suffering from schizophrenia (Category of evidence B, Recommendation grade 3). – There is no evidence to support the combination of galantamine and risperidone depot for the treatment of cognitive symptoms in schizophrenia (Category of evidence E). – In summary, there is good evidence to support the use of long-acting injectable paliperidone for the treatment of schizophrenia (Category of evidence A, Recommendation grade 1). – There is no evidence that allows us to state a superiority of the depot compared to oral paliperidone (Category of evidence A, Recommendation grade 1). – Paliperidone depot seems to be as effective as risperidone depot

	(Category of evidence A, Recommendation grade 1). – There is good evidence to support the use of long-acting injectable olanzapine (Category of evidence (A)/B, Recommendation grade (2)/3). – It should be mentioned that we were not able to identify a comparator study between olanzapine pamoate and another depot antipsychotic. – The postinjection delirium sedation syndrome needs to be considered as a possible severe side effect after every injection. – Each injection should follow the rules of action described by the manufacturer and after each injection, a three hour observation period needs to be respected (Category of evidence C, Recommendation grade 4). – Antipsychotics do improve quality of life in schizophrenia patients, but no evidence can be found in favour of one particular antipsychotic drug or a group (Category of evidence A, Recommendation grade 1). – However, it should be mentioned that side effects do infl uence quality of life and that both the reduction and careful management of side effects are important in order to improve quality of life (Category of evidence C, Recommendation grade 4). – There is some evidence that subjective wellbeing is greater following treatment with certain SGAs, as discussed above (Category of evidence B, Recommendation grade 3).

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 18.10.2017

#	Suchfrage
#1	[mh Schizophrenia [mj]]
#2	(Schizophren* or "dementia praecox"):ti
#3	#1 or #2
#4	#3 Publication Year from 2012 to 2017

SR, HTAs in Medline (PubMed) am 18.10.2017

#	Suchfrage
1	"schizophrenia/therapy"[MeSH Terms]
2	(Schizophren*[Title] OR "Dementia Praecox"[Title])
3	((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract]
4	(#2 AND #3)
5	(#1 OR #4)
6	(#5) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
7	(#5) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
8	(#6 OR #7)
9	(#8) AND ("2012/10/01"[PDAT] : "2017/10/18"[PDAT])
10	(#9) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 18.10.2017

#	Suchfrage
1	schizophrenia[MeSH Major Topic]
2	(Schizophren*[Title] OR "Dementia Praecox"[Title])
3	#1 OR #2
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
5	(#4) AND ("2012/10/01"[PDAT] : "2017/10/18"[PDAT])

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Anhang:

Table DS1 Included studies

Paper[1]	Duration[2]	Country	Setting[3]	Diagnostic tool[4]	TRS criteria deviation[5]	Control Medication[6]	Mean Age (SD) for Clozapine / Control[7]	Number of Participants Clozapine / Control	CPZ equivalent control (SD)[8]	CPZ equivalent clozapine (SD)	Allocation[911]	Blinding[10]	Randomisation[11]	Primary Outcome[12]	Reporting[13]	ITT[1416]	Other Bias[1517]
Azorin et al 2001	12 w	France & Canada	H+C	DSM-IV	One Trial, intolerance	Risperidone A	37.8 (10.4) / 39.5 (11.3)	138 / 135	NS	NS	NS	Double	Yes	Yes	Yes	Yes	Pharma clozapine
Bitter et al 2004	18 w	Hungary & South Africa	H	DSM-IV	One Trial, intolerance	Olanzapine A	37.6 *	72 / 72	441 (102)	224 (100)	NS	Double	Yes	Yes	Yes	Yes	Pharma control
Bondolfi et al 1998	8 w	Switzerland	C	DSM-III-R	No Dose, intolerance	Risperidone A	36.2 (12.2) / 38.3 (12.9)	43 / 43	NS	NS	NS	Double	Yes	Yes	Yes	Yes	Pharma control
Buchanan et al 1998	10 w	USA	C	DSM-III-R	No deviation	Haloperidol T	41.0 (6.4) / 40.1 (7.9)	38 / 37	1124 (334)	474 (50)	Yes	Double	Yes	Yes	Yes	Yes	Pharma clozapine & control
Cao et al 2003	12 w	China	H	ICD 10	No deviation	Risperidone A	36.9 (7.9) / 37.5 (8.7)	30 / 30	NS	NS	NS	Double	Yes	Yes	Yes	Yes	FNS
Hong et al 1997	12 w	China	H	DSM-IV	No deviation	Chlorpromzaine T	39.7 (8.4) / 37.1 (8.7)	21 / 19	1163 (228)	641 (155)	Yes	Double	Yes	Yes	Yes	Yes	No
Kane et al 1988	6 w	USA	H	DSM-III	No deviation	Chlorpromzaine T	35.7 (8.87)*	37 / 34	NS	NS	NS	Double	NS	Yes	Yes	Yes	Pharma clozapine
Kane et al 2001	29 w[16]	USA	H + C	DSM-III-R	No deviation	Haloperidol T	41 (10) / 40 (8)	126 / 141	900 (334)	523 (171)	Yes	Double	Yes	Yes	Yes	No	No
Kumra et al 1996	6 w	USA	H	DSM-III-R	No Dose or Duration, intolerance	Haloperidol T	14.4 (3.0) / 13.7 (1.6)	10 / 11	718 (378)	176 (145)	Yes	Double	Yes	Yes	Yes	Yes	No
Kumra et al 2008	12 w	USA	not stated	DSM-IV	No Dose or Duration	Olanzapine A	15.8 (2.2) / 15.5 (2.1)	18 / 21	716 (144)	461 (207)	Yes	Double	Yes	Yes	Yes	Yes	No
McEvoy et al 2006	78 w[17]	USA	C	DSM-IV	One Trial & no Dose, intolerance	Olanzapine A Risperidone A Quetiapine A	39.4 (9.9) / 44.3 (10.5) / 37.1 (11.8) / 39.7 (10.4)	43 / 17 / 14 / 14	629 (180) 398 (97) 589 (145)	368 (154)	NS	Clozapine single, control double	Yes	Yes	Yes	Yes	No
Meltzer et al 2008	26 w[18]	USA	C	DSM-IV	No Dose	Olanzapine A	37.2 (9.2) / 36.4 (11.1)	21 / 19	953 (270)	680 (256)	Yes	Double	NS	Yes	Yes	No	Pharma control
Moresco et al 2004	8 w	Italy	H	DSM-IV	No deviation	Olanzapine A	38.3 (9.1) / 34.1 (7.6)	12 / 11	474 (8)	359 (6)	Yes	Double	NS	Yes	Yes	No	Pharma control
Naber et al 2005	26 w	Germany	H+C	DSM-IV	One Trial & no Dose, intolerance	Olanzapine A	35.2 (10.8) / 32.9 (10.4)	57 / 57	412 (102)	215 (82)	NS	Double	Yes	Yes	Yes	Yes	Pharma control
Rosenheck et al 1997	52 w[19]	USA	H+C	DSM-III-R	Intolerance	Haloperidol T	43.2 (7.7) / 43.9 (8.3)	205 / 218	NS	NS	NS	Double	Yes	Yes	Yes	Yes	No
Sacchetti et al 2009	18 w	Italy	C	DSM-IV	Intolerance	Ziprasidone A	38.3 (11.2) / 41.6 (10.2)	74 / 73	450 (31)	386 (52)	NS	Double	Yes	Yes	Yes	No	Pharma control
Shaw et al 2006	8 w	USA	H	K-SADS §	<4 week Duration >100mg CPZ equivalent, intolerance	Olanzapine A	12.8 (2.4) / 11.7 (2.3)	12 / 13	468 (90)	362 (106)	Yes	Double	Yes	Yes	Yes	Yes	FNS
Tollefson et al 2001	18 w	Multiple[20]	C	DSM-IV	>500mg CPZ equivalent, intolerance	Olanzapine A	38.6 (10.6)*	90 / 90	450 (55)	332 (101)	NS	Double	NS	Yes	Yes	Yes	Pharma control
Volavka et al 2002	14 w[21]	USA	H	DSM-IV	One Trial	Olanzapine A Risperidone A Haloperidol T	40.8 (9.2)*	40 / 41 / 39 / 37	513 (39) 683 (163) 837 (157)	459 (158)	Yes	Double	Yes	Yes	Yes	Yes	Pharma control
Wahlbeck et al 2000	10 w	Finland	H+C	DSM-IV	Intolerance	Risperidone A	35.7 (9.8) / 36.8 (9.8)	11 / 9	673 (163)	437 (227)	Yes	Single	Yes	Yes	Yes	Yes	No
Wang et al 2002	12 w	China	H	CCMD-3	No Dose	Risperidone A	35.6 (7.5) / 36 (7.5)	35 / 35	NS	NS	NS	Single	Yes	Yes	Yes	Yes	FNS

NS=not stated

[1] Lead author and year of publication
[2] w=weeks
[3] H = Hospital, C = Community
[4] DSM = Diagnostic and Statistical Manual, ICD = International Classification of Diseases, K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children CCMD-3 = Chinese classification of mental disorder
[5] TRS= Treatment Refractory Schizophrenia. Table lists areas in which study varied from definition of TRS criteria of failed treatment: Trial of ≥2 antipsychotics; Duration ≥ 6 weeks each; Dose over 600mg/day chlorpromazine (CPZ) equivalents); trials not shortened because of intolerable side effects.
[6] A=Atypical antipsychotic, T=Typical antipsychotic
[7] SD= Standard Deviation, * = mean age and SD not provided for both clozapine and control
[8] Mean chlorpromazine equivalent dose and standard deviation of control medication and clozapine using power transformation formula from Andreason et al (2010)
[9] Adequate allocation concealment
[10] Single is to assessor only
[11] Adequate Random Sequence Generation
[12] Primary Outcome Measures were pre-specified and reported