[Updated 2015]

Role of depot antipsychotic medication in long-term antipsychotic treatment

SCOPING QUESTION: In individuals with psychotic disorders (including schizophrenia) who require long-term antipsychotic treatment, what is the safety and role of depot antipsychotic medication?

BACKGROUND

Psychotic disorders (including schizophrenia) are the most disabling mental disorders and require a disproportionate share of mental health services (Mueser and McGurk, 2004). The lifetime prevalence of schizophrenia is around 1% (Jablensky, 1997) and the incidence is quite similar across countries (Taitt, 1979). Disability and impairment in functioning can be profound, resulting in the need for assistance in meeting basic living needs. Wide variation occurs in the course of psychotic disorders, but they are generally chronic, punctuated by relapses of severe psychotic symptoms that have disruptive effects on many life domains (Häfner et al., 2003). Therefore, relapse prevention is a major goal of treatment (Mueser and McGurk, 2004).

Antipsychotic medications are the mainstay of pharmacological treatment for patients with psychotic disorders and there is evidence of antipsychotic efficacy for relapse prevention, with the risk of relapse is 2–6 times higher without medication (Robinson et al., 1999). However non-adherence is reported to occur in up to 50% of patients with psychotic disorders (Sendt et al., 2015). Long-acting depot antipsychotic medications were developed in the 1960s to promote adherence in people with recurrent psychotic disorders, including schizophrenia. Depot antipsychotics simplify the treatment process, are believed to enhance treatment adherence (Kaplan et al., 2013; Kishimoto et al., 2013) and eliminate bioavailability problems, as well as the risk of overdose. However, only a minority of patients receive depot antipsychotics and reasons for underutilization may include negative attitudes, perceptions and beliefs of both patients and health care professionals (Kaplan et al., 2013). There are also concerns over adverse effects of depot antipsychotics, lack of flexibility of administration and low patient acceptance.

The 2010 WHO mhGAP Intervention Guidelines recommend to consider depot injectable antipsychotic with a view to improve adherence only if the response is inadequate to more than one antipsychotic medication. However, in the last five years there have been new large controlled trials comparing depot with oral antipsychotics; therefore, an update of the scoping question is essential in order to confirm or change the recommendation.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults with psychotic disorders (including schizophrenia)
- **Interventions:** Depot antipsychotic medications
- **Comparison:** Oral antipsychotics medications
- **Outcomes:**
  - **Critical** – Symptoms severity, prevention of relapses, adverse effects of treatment
  - **Important** – Treatment adherence, disability and functioning

Search strategy

The search was conducted in Week 30 of 2014 using the following databases: Cochrane Database of Systematic Reviews, PubMED (clinical queries), the Campbell Collaboration, LILACS, psycINFO, Embase and PILOTS. Keywords used included: *"long-acting antipsychotic* OR depot antipsychotic*" AND "systematic review"*.

In databases that allowed specifically for selection of systematic reviews and meta-analyses (e.g. PubMed, psycINFO and Embase) this was selected option and used only the keyword *"long-acting antipsychotic* OR depot antipsychotic*"*. Studies were included only if they were systematic reviews or meta-analyses of randomized controlled trials (RCTs) with adults (>18 years) comparing depot with oral antipsychotics and published from 2010 onwards.

Systematic reviews included in GRADE tables or footnotes

- Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, Borenstein M, Kane JM, Correll CU (2014). Long-Acting Injectable vs Oral Antipsychotics for Relapse Prevention in Schizophrenia: A Meta-Analysis of Randomized Trials. Schizophrenia Bulletin.40(1):192-213. doi:10.1093/schbul/sbs150.

- Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S (2011). Oral versus depot antipsychotic medications for schizophrenia--a critical systematic review and meta-analysis of randomised long-term trials. Schizophrenia Research.127(1-3):83-92. doi:10.1016/j.schres.2010.11.020.

Excluded from GRADE tables and footnotes

Adams CE, Fenton MK, Qurashi S, David AS (2001). Systematic meta-review of depot antipsychotic medications for people with schizophrenia. British Journal of Psychiatry.179:290-299.
REASON FOR EXCLUSION: Kishimoto et al. (2014) included all pertinent studies.

PICO Table

Population: Adults with psychotic disorders (including schizophrenia)					
Intervention	**Comparison**	**Outcome**	**Systematic reviews used for GRADE**	**Justification for systematic review used**	**Relevant GRADE table**
Depot antipsychotic medications	Oral antipsychotics medications	Symptoms severity	Kishimoto et al. (2014)	These are the most recent and comprehensive high quality systematic reviews.	Table 1
		Long-term	Leucht et al. (2011) (long-term outcomes)		Table 2
		Prevention of relapses	Kishimoto et al. (2014)	These are the most recent and comprehensive high quality systematic reviews.	Table 1
		Long-term	Leucht et al. (2011) (long-term outcomes)		Table 2
		Adverse effects of treatment	Kishimoto et al. (2014)	These are the most recent and comprehensive high quality systematic reviews.	Table 1
		Long-term	Leucht et al. (2011) (long-term studies)		Table 2
		Disability and functioning	No evidence available		N/A

		Treatment adherence	Kishimoto et al. (2014)	These are the most recent and comprehensive high quality systematic reviews.	Table 1
		Long-term	Leucht et al. (2011) (long-term studies)		Table 2

Narrative description of the studies that went into the analysis

Kishimoto et al. (2014) included 21 studies randomizing 5176 patients with schizophrenia or related disorders to intramuscular depot or oral formulations of antipsychotic medications. The number of patients per study ranged from 31–921 (median 105), with a mean study duration of 66 ± 32 weeks. Nine studies were double-blind, five were rater-masked and seven were open. Depot antipsychotics examined were fluphenazine (N=8), haloperidol (N=1), zuclopenthixol (N=1), risperidone (N=9) and olanzapine (N=2). The oral comparators were fluphenazine (N=4), pimozide (N=2), haloperidol (N=1), trifluoperazine (N=1), zuclopenthixol (N=1), olanzapine (N=4), quetiapine (N=2), risperidone (N=2), aripiprazole (N=2) and other antipsychotic (N=3). There were 13 studies that included only outpatients, two which included inpatients at baseline who were discharged shortly after study initiation, one study requiring patients to be hospitalized throughout the trial, and five studies provided insufficient information.

Leucht et al. (2011) included 10 long-term studies randomizing 1700 patients with schizophrenia or related disorders to intramuscular depot or oral formulations of antipsychotic medications. As people with schizophrenia often do not relapse immediately after stopping medication, only long-term studies defined as 1 year or longer were included. Fluphenazine depot was examined in six studies (n=584), risperidone long-acting-injectable in two studies and haloperidol-decanoate and zuclopenthixol-depot were examined in one study each. The oral comparators were fluphenazine (N=4), pimozide (N=2), zuclopenthixol (N=1), quetiapine (N=1), olanzapine (N=1) and any antipsychotic (N=1). The doses applied varied and overall were somewhat higher in older trials. All participants were remitted or at least partly remitted at baseline. There were participants recruited when they were still in the hospital in five studies, but they were outpatients during the maintenance phase of the trial. There were 951 men and 667 women, the participants' mean age was 36±7 years and the mean illness duration ranged between 4 and 17 years.

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GRADE Tables

Table 1. Depot antipsychotics vs. oral antipsychotics for treatment of psychotic disorders

Authors: L Tarsitani and C Barbui
Question: Should depot antipsychotics vs. oral antipsychotics be used for treatment of psychotic disorders (including schizophrenia)?
Bibliography: Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, Borenstein M, Kane JM, Correll CU (2014). Long-Acting Injectable vs Oral Antipsychotics for Relapse Prevention in Schizophrenia: A Meta-Analysis of Randomized Trials. Schizophrenia Bulletin.40(1):192-213. doi:10.1093/schbul/sbs150.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Depot antipsychotics**	**Oral antipsychotics**	**Relative (95% CI)**	**Absolute**		
Symptoms severity (hospitalization; follow-up 24-130 weeks[1])												
10[2]	Randomized trials	Serious[3,4]	No serious inconsistency	Serious[5]	No serious imprecision	None	248/1179 (21%)	305/1117 (27.3%)	RR 0.88 (0.75 to 1.03)[6]	33 fewer per 1000 (from 68 fewer to 8 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Symptoms severity (medication inefficacy: relapse + dropout due to inefficacy; follow-up 24-130 weeks[1])												
21[2]	Randomized trials	Serious[3]	Serious[7]	Serious[5]	No serious imprecision	None	571/2600 (22%)	601/2369 (25.4%)	RR 0.97 (0.82 to 1.15)[6]	8 fewer per 1000 (from 46 fewer to 38 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Prevention of relapses (relapse rate - longest time point; follow-up 24-130 weeks[1])												
21	Randomized trials	Serious[3]	Serious[8]	Serious[5]	No serious imprecision	None	671/2596 (25.8%)	739/2354 (31.4%)	RR 0.93 (0.8 to 1.08)[6,9]	22 fewer per 1000 (from 63 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		

Disability and functioning												
0	No evidence available					None	-	-	-	-		IMPORTANT
								0%		-		
Adverse events (droputs due to adverse events; follow-up 24-130 weeks[1])												
19[10]	Randomized trials	Serious[11]	No serious inconsistency	Serious[5]	No serious imprecision	None	93/2455 (3.8%)	76/2207 (3.4%)	RR 1.10 (0.74 to 1.64)[6]	3 more per 1000 (from 9 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Treatment adherence (all-cause discontinuation; follow-up 24-130 weeks[1])												
20	Randomized trials	Serious[12]	Serious[13]	Serious[5]	No serious imprecision	None	963/2556 (37.7%)	908/2326 (39%)	RR 1.03 (0.9 to 1.18)[6]	12 more per 1000 (from 39 fewer to 70 more)	⊕OOO VERY LOW	IMPORTANT
								0%		-		
Treatment adherence (non-adherence; follow-up 24-130 weeks[1])												
10[14]	Randomized trials	Serious[4]	No serious inconsistency	Serious[5]	Serious[15]	None	55/955 (5.8%)	73/1063 (6.9%)	RR 0.77 (0.49 to 1.22)[6]	16 fewer per 1000 (from 35 fewer to 15 more)	⊕OOO VERY LOW	IMPORTANT
								0%		-		

[1] Mean study duration was 66 ± 32 weeks.
[2] From Kishimoto et al. (2014) Supplementary Figure 8.
[3] In 9 out of 21 studies dropout rate is > 30% (long-term studies); 7 studies were open-label.
[4] In 6 out of 10 studies dropout rate is > 30% (long-term studies).
[5] Patients who are reluctant to take oral antipsychotics are not included in trials.
[6] Estimates < 1 are in favour of depot antipsychotics.
[7] I^2= 57%.
[8] I^2= 58%.
[9] In supplementary material, similar figures are reported for relapse rate at 3 months (RR 0.90, 0.70 to 1.17); 6 months (RR 0.93, 0.76 to 1.14); 12 months (RR 0.90, 0.75 to 1.08); 18 months (RR 0.87, 0.67 to 1.13); and 24 months (RR 0.92, 0.71 to 1.19).
[10] From Kishimoto et al. (2014) Supplementary Figure 7.
[11] In 9 out of 19 studies dropout rate is > 30% (long-term studies); 7 studies were open-label.
[12] In 9 out of 20 studies dropout rate is > 30% (long-term studies); 7 studies were open-label.
[13] I^2= 58%.
[14] From Kishimoto et al. (2014) Supplementary Figure 10.
[15] CI includes no effect and appreciable benefit.

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Table 2. Depot antipsychotics vs. oral antipsychotics for treatment of psychotic disorders (in long-term studies of 1 year or more)

Authors: L Tarsitani and C Barbui
Question: Should depot antipsychotics vs. oral antipsychotics be used for treatment of psychotic disorders (including schizophrenia) (in long-term studies of 1 year of more)?
Bibliography: Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S (2011). Oral versus depot antipsychotic medications for schizophrenia--a critical systematic review and meta-analysis of randomised long-term trials. Schizophrenia Research.127(1-3):83-92. doi:10.1016/j.schres.2010.11.020.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Depot antipsychotics	Oral antipsychotics	Relative (95% CI)	Absolute		
Symptoms severity – Rehospitalization (follow-up 52-104 weeks)												
7	Randomized trials	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	102/745 (13.7%)	136/731 (18.6%)	RR 0.78 (0.57 to 1.05)[3]	41 fewer per 1000 (from 80 fewer to 9 more)	⊕⊕OO LOW	CRITICAL
Symptoms severity – Dropout due to inefficacy (follow-up 52-104 weeks[4])												
9	Randomized trials	Serious[5]	No serious inconsistency	Serious[2]	No serious imprecision	Reporting bias[6]	142/688 (20.6%)	276/692 (39.9%)	RR 0.71 (0.57 to 0.89)[3]	116 fewer per 1000 (from 44 fewer to 172 fewer)	⊕OOO VERY LOW	CRITICAL
Prevention of relapses (follow-up 52-104 weeks[4])												
10	Randomized trials	Serious[7]	No serious inconsistency	Serious[2]	No serious imprecision	Reporting bias[8]	182/843 (21.6%)	276/829 (33.3%)	RR 0.70 (0.57 to 0.87)[3]	100 fewer per 1000 (from 43 fewer to 143 fewer)	⊕OOO VERY LOW	CRITICAL
Disability and functioning												
0	No evidence					None	-	-	-	-		IMPORTANT

	available							0%		-		
Adverse events – Dropout due to adverse events (follow-up 52-104 weeks)												
7	Randomized trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[9]	None	35/688 (5.1%)	26/692 (3.8%)	RR 1.34 (0.7 to 2.58)[3]	13 more per 1000 (from 11 fewer to 59 more)	⊕OOO VERY LOW	CRITICAL
Treatment adherence – Non-adherence (follow-up 52-104 weeks)												
5	Randomized trials	Serious[10]	Serious[11]	Serious[2]	Serious[9]	None	44/567 (7.8%)	55/574 (9.6%)	RR 0.76 (0.37 to 1.56)[3]	23 fewer per 1000 (from 60 fewer to 54 more)	⊕OOO VERY LOW	IMPORTANT
Treatment adherence – Total dropouts (follow-up 52-104 weeks)												
8	Randomized trials	Serious[12]	No serious inconsistency	Serious[2]	No serious imprecision	None	342/633 (54%)	384/642 (59.8%)	RR 0.90 (0.81 to 1.01)[3]	60 fewer per 1000 (from 114 fewer to 6 more)	⊕OOO LOW	IMPORTANT

[1] In 4 out of 7 studies dropout rate is > 30% (long-term studies), blindness is at high risk of bias in 1 study according to Leucht et al. (2011) and 2 studies are open-label.
[2] Patients who are reluctant to take oral antipsychotics are not included in trials.
[3] Estimates < 1 are in favour of depot antipsychotics.
[4] Seven studies lasted 52 weeks and three studies lasted104 weeks.
[5] In 6 out of 9 studies dropout rate is > 30% (long-term studies), blindness is at high risk of bias in 2 studies according to Leucht et al. (2011) and 2 studies are open-label.
[6] High risk of selective reporting in 3 out of 9 studies and high risk of "other bias" in 8 out of 9 studies according to Leucht et al. (2011).
[7] In 6 out of 10 studies dropout rate is > 30% (long-term studies), is at high risk of bias in two studies according to Leucht et al. (2011) and 3 study are open label.
[8] High risk of selective reporting in 3 out of 10 studies and high risk of "other bias" in 8 out of 10 studies according to Leucht et al. (2011).
[9] CI includes no effect and appreciable benefit.
[10] In 4 out of 5 studies dropout rate is > 30% (long-term studies), blindness is at high risk of bias in 1 study according to Leucht et al. (2011) and 1 study is open-label.
[11] $I^2 = 58\%$.
[12] In 6 out of 8 studies dropout rate is > 30% (long-term studies), blindness is at high risk of bias in 1 study according to Leucht et al. (2011) and 2 studies are open-label.

Additional evidence not mentioned in GRADE tables

The following studies were identified as relevant to the scoping question:

Kirson NY, Weiden PJ, Yermakov S, Huang W, Samuelson T, Offord SJ, Greenberg PE, Wong BJ (2013). Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: Synthesizing results across different research designs. Journal of Clinical Psychiatry.74(6):568-575. doi:10.4088/JCP.12r08167.

Kirson et al. (2013) summarized six RCTs, five prospective studies and eight retrospective studies on depot-oral antipsychotics comparisons in patients with schizophrenia or similar disorders. Depot antipsychotics examined were fluphenazine, haloperidol olanzapine, perphenazine, risperidone and zuclopenthixol. Meta-analysis of adjusted RR by study design for mixed outcomes (including relapse, discontinuation and hospitalization) showed no benefit of depot over oral formulations in RCTs (RR 0.89, 0.64 to 1.22). However, a significant advantage for depot formulations was found in other study designs (prospective RR 0.62, 0.48 to 0.81; retrospective RR 0.56, 0.44 to 0.71).

Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU (2013). Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. Journal of Clinical Psychiatry.74(10):957-965. doi:10.4088/JCP.13r08440.

Kishimoto et al. (2013) performed a systematic review and meta-analysis of 25 mirror-image studies from 28 countries involving 5940 patients with schizophrenia for more than 12 months. Mirror-image studies compared periods of oral versus depot antipsychotic treatment in the same patients. Included outcomes were hospitalization risk, number of hospitalizations, hospitalization days and length of stay in the hospital. A significant advantage for depot formulations was found in preventing hospitalization (16 studies, N = 4066; RR 0.43, 0.35 to 0.53) and in decreasing the number of hospitalizations (15 studies; RR 0.38, 0.28 to 0.51). Given the possible biases in mirror-image studies (such as expectation bias, natural illness course and time effect), a cautious interpretation is required.

National Collaborating Centre for Mental Health (NCCMH). 2007. Antenatal and postnatal mental health: Clinical management and service guidance. [CG45]. London: National Institute for Health and Care Excellence (NICE).

The recommendations of this guideline include that depot antipsychotics should not be routinely prescribed to pregnant women because there is relatively little information on their safety and infants may show extrapyramidal symptoms several months after administration of the depot. These are usually self-limiting.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Quantitative summary of evidence table

Outcomes	**Depot antipsychotics vs. oral antipsychotics** *(Number of studies, RR [95% CI], quality)*	**Depot antipsychotics vs. oral antipsychotics (in long-term studies only)** *(Number of studies, RR [95% CI], quality)*
Symptoms severity – Hospitalization	10 studies, RR 0.88 (0.75 to 1.03) No difference, LOW quality	7 studies, RR 0.78 (0.57 to 1.05) No difference, LOW quality
Symptoms severity – Relapse/dropout due to inefficacy	21 studies, RR 0.97 (0.82 to 1.15) No difference VERY LOW quality	9 studies, RR 0.71 (0.57 to 0.89) In favour of depot antipsychotics, VERY LOW quality
Prevention of relapses	21 studies, RR 0.93 (0.8 to 1.08) No difference VERY LOW quality	10 studies, RR 0.70 (0.57 to 0.87) In favour of depot antipsychotics, VERY LOW quality
Disability and functioning	N/A	N/A
Adverse events	19 studies, RR 1.10 (0.74 to 1.64) No difference, LOW quality	7 studies, RR 1.34 (0.7 to 2.58) No difference, VERY LOW quality
Treatment adherence - non adherence	10 studies, RR 0.77 (0.49 to 1.22) No difference, VERY LOW quality	5 studies, RR 0.76 (0.37 to 1.56) No difference, VERY LOW quality
Treatment adherence - total dropouts	20 studies,	8 studies,

	RR 1.03 (0.9 to 1.18) No difference, VERY LOW quality	RR 0.90 (0.81 to 1.01) No difference, LOW quality

Evidence to recommendation table

Benefits	There is evidence showing that depot antipsychotics are similarly effective in comparison with oral preparations, in terms of hospitalizations and dropouts due to inefficacy and/or relapse. Similarly, in terms of both treatment adherence and proportion of patients who relapsed, there is evidence suggesting that depot antipsychotics are similarly effective than oral antipsychotics in psychotic disorders including schizophrenia. When only long-term studies are considered, depot antipsychotics are more effective in reducing dropouts due to inefficacy when compared with oral antipsychotics. In terms of long-term relapse prevention, there is evidence that depot antipsychotics are significantly more effective than oral antipsychotics. In terms of long-term treatment adherence, depot and oral antipsychotics are similarly effective in terms of total dropouts and treatment adherence. There is no evidence is available on disability and functioning, quality of life and satisfaction with care.
Harms	The evidence suggests that depot antipsychotics do not differ in terms of dropouts for adverse events when compared to oral preparations. Long-term studies found no differences between depot and oral antipsychotic preparations in dropout for adverse events. In terms of mortality, there is no evidence is available.

Summary of the quality of evidence	The quality of evidence was LOW or VERY LOW for all outcomes considered.

Value and preferences	
In favour	Important issues include the consequences of covert non-adherence (intentional or not) to oral daily treatment that may lead to psychotic relapses, as well as the risk of bioavailability problems with oral antipsychotics. Additionally, there is no risk of intentional or non intentional overdose with depot injected treatments. The use of depot preparations may be beneficial to patients, their families and caretakers by reducing the daily use of medication and supervision of treatment adherence.
Against	There are significant concerns about the long-term safety and tolerability associated with depot antipsychotic medications. In the long-term, possible adverse effects of depot antipsychotics include tardive dyskinesia, movement disorders and injection site reactions. Treatment cannot be rapidly withdrawn if adverse effects develop with depot preparations. There are also concerns about lack of flexibility of administration and low patient acceptance of the depot injection because it can be perceived as a discriminating and passive experience. However, in some cultures, medicines-by-injecting route are assumed to be more 'potent' than oral route. Depot antipsychotic medicines may have the risk of being administered forcibly against the consent the patient, which is cause for human rights concerns.
Uncertainty or variability?	There is variability with regards to patient preferences in the use of depot preparations in contrast with oral medication

Feasibility (including resource use considerations)	In many low- and middle-income countries, continuous availability of antipsychotic medicines in non-specialized health care is a challenge; therefore, depot preparations may have the advantage of requiring a smaller quantity of medications per year. Depot formulation can be beneficial for treatment adherence in settings where there is low human resource availability to provide continued care through follow up or where access to care is difficult. In many countries, the per day cost may be reduced with the use of depot preparations. In some countries, the cost of second-generation depot preparations is much higher, which may preclude their use. In many countries, the availability of health care staff needed to administer an injection may be a significant barrier to delivering these interventions. Use of depot preparations requires the patient and families to return to the health care facility at regular intervals, facilitating psychosocial interventions. Fluphenazine decanoate or enantate is available on the WHO Essential Medicine List.
Uncertainty or variability?	There is variability in terms of the availability of depot preparations and capacity to administer these interventions, which may vary across health care and country settings.

[Updated 2015]

Recommendation and remarks

Recommendation

In people with psychotic disorders (including schizophrenia) requiring long-term antipsychotic treatment, depot antipsychotics can be offered instead of oral medications as part of a treatment plan.

Rationale: Although the quality of the evidence is low to very low, the benefits of depot versus antipsychotics are similar in terms of hospitalizations and dropouts due to inefficacy. In terms of long-term relapse prevention, there is evidence that depot antipsychotics are significantly more effective than oral antipsychotics. The evidence also suggests that depot antipsychotics do not differ in terms of dropouts for adverse events when compared to oral preparations.

Remarks

Patients and carers should be offered clear and accessible information in a suitable format regarding the use and possible side effects of oral versus depot preparations.

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Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High □ Moderate □ Low **X Very low**
Balance of benefits versus harms	**X Benefits clearly outweigh harms** □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits
Values and preferences	□ No major variability **X Major variability**
Resource use	**X Less resource-intensive** □ More resource-intensive
Strength	**CONDITIONAL**

OTHER REFERENCES

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