Systematic Review and Meta-analysis of Anticholinergic Side Effects of Long-acting Antipsychotics

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Abstract: *Background:* There are few studies on the anticholinergic side effects of long-acting antipsychotics. They tend to be used with stigmatized, severely ill and non-concordant patients rather than first episode psychosis.

Aim: To investigate prevalence/incidence rate of anticholinergic side effects of long-acting antipsychotics.

Methods: We included all participants with schizophrenia, schizoaffective disorder or schizotypal disorder on depot antipsychotics in the trials within all Cochrane reviews published by the Cochrane schizophrenia group. A search was undertaken in the Cochrane Database and data extracted into Microsoft Excel to analyze frequencies, prevalence and confidence intervals of the anticholinergic side effects of all identified long-acting antipsychotic medications.

Result: We found seven reviews for seven depot antipsychotics. For example for fluphenazine decanoate at least a quarter of the participants experienced blurred vision 24.5% (CI 11 to 47) in the short-term, 16 % (CI 10-27) in the medium-term, and 21.4 % (CI 16-28) in the long-term.

Conclusion: The anticholinergic side effects of long-acting depot antipsychotics are not any more frequent than the anticholinergic side effects of oral antipsychotics. There is no evidence to suggest that oral medications are better tolerated than long-acting depot preparations.

Keywords: Long-acting antipsychotics, depot, schizophrenia, anticholinergic side effects, blurred vision, dry mouth, constipation.

INTRODUCTION

Patients with first episode schizophrenia usually respond well to treatment [1]. However, relapses even during the first year of the course of the illness are frequent and many times associated with their clinical deterioration [2].

Long-acting injections are generally used with people who experience significant complications of non-concordance, e.g. relapse and often re-hospitalization. There is no published head-to-head comparison of outcomes among first-episode patients receiving drugs with long-acting injections and those receiving oral medication. However, non-adherence is a considerable problem with first-onset psychosis [3].

In spite of all the support and monitoring, non-concordance to medication leading to relapse is very common and this issue could be addressed by using long-acting depot antipsychotics to aid compliance in this group of generally young patients in their 20s. However, the conventional antipsychotic depot injections are not free of side effects which happen to be a common reason for discontinuation of the medication. Although clinicians often focus on the extrapyramidal side effects of antipsychotics, the anticholinergic side effects can also be problematic. We will examine these in more detail and compare the anticholinergic side effect profiles of the identified antipsychotics.

A previous search by M.O. [4] in Embase, PsychInfo, Medline identified three quantitative studies on anticholinergic side effects [5-7]. Following this a systematic overview of anticholinergic side effects over the short-term was published [8]. However, there is no study which has systematically investigated anticholinergic side effects of Cochrane reviews for depot antipsychotics over the short-, medium- and long-term.

AIM

We aim to systematically investigate incidence/prevalance rates of anticholinergic side effects for long-acting depot antipsychotics over short-, medium- and long-term.

METHODS

Criteria for Considering Reviews for This Study

The included studies were any systematic review undertaken by the Cochrane Schizophrenia Group with at least one of the arms having long-acting antipsychotic depot. The type of participants were anyone with a diagnosis of schizophrenia, schizophreniform disorder, schizotypal disorder diag-

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nosed using any diagnostic criteria irrespective of gender, age or ethnicity that were treated with depot antipsychotic medications. The outcome measures were the prevalence/incidence of the anticholinergic side effects: - Blurred vision, constipation, dry mouth, urinary retention, nasal stuffiness, hyperthermia, increased salivation, tachycardia and confusion.

Search Method for Identifying of The Studies

Cochrane library was searched by M.O. using the search term hm-schiz in 'search all text' in 2007. The titles of all reviews identified by this way were retrieved and those relevant for pharmacological care were selected. The reviews which met the inclusion criteria were included. Rejected reviews were recorded with reason for rejection.

M.O. extracted all the data from the full text articles using data extraction forms and entered the data into an excel spreadsheet. Dummy tables were constructed to guide analysis. The data was grouped into short-term (up to 3 months), medium-term (3 to 6 months), and long-term (over 6 months). Unclear issues were resolved by discussion with the supervisor (C.E.A). If any issues remained which could not have been resolved with the above steps, the original studies have been re-inspected. The problem with data extractions of such studies has been detailed in the previous study [8]. Simple frequencies, proportions and confidence intervals were calculated using the method recommended by Wilson [9].

RESULTS

In total 7 reviews of depot antipsychotics were included. In addition there were some data on depot antipsychotics from 46 reviews which compared oral drugs with other typicals or atypicals but did not specifically mention that they used depot. We included only the trials arms which reported data on depot medications.

There were data on anticholinergic side effects for bromperidol depot, flupenthixol depot, depot fluphenazine, fluspirilene decanoate, depot methylperidol, depot pipotiazine palmitate and long-acting risperidone.

Although many of these reviews did include studies reporting anticholinergic effects, they also included studies in which anticholinergic effects were not reported. For example, in the review 'Depot flupenthixol decanoate for schizophrenia and other psychotic disorder' only two out of the 15 included studies reported anticholinergic effects. 13 out 15 included studies had no data reported or recorded.

There were data on placebo side effects reported for the short-, medium- and long-term. The data from placebo are from oral as well as from depot medications. They represent non-specific effects of medications.

Anticholinergic side effects reported with depot antipsychotics in the short-term were mainly blurred vision, constipation and dry mouth. Nearly a quarter of the patients experienced blurred vision with flupenthixol and fluphenazine and with one sixth of the patients on fluspirilane decanoate (less with pipothiazine). Over a third of the patients experienced constipation with fluphenazine and fluspiriline long-acting injections, whereas bromperidol, metylperidol, risperidone and flupenthixol depot were less constipating. Nearly a quarter of the patients experienced dry mouth with fluphenazine and long-acting risperidone and one sixth of the patients on fluspirilane decanoate. However, bromperidol and pipotiazine depot and methylperidol were less of a cause for dry mouth and not much different to placebo. There were data on increased salivation, tachycardia and urinary retention in the short-term with risperidone, fluphenazine, bromperidol and methylperidol but these figures were comparable to that of placebo. Surprisingly, nasal stuffiness, hyperthermia and confusion were only reported in the placebo arms in the short-term (Table **1**).

In the medium-term blurred vision was significantly higher with fluphenazine. Blurred vision was comparable to placebo with fluspirilene decanoate and flupenthixol decanoate. Similarly, dry mouth was comparable to placebo with bromperidol, fluspirilene decanoate and fluphenazine. For other depot medications for this side effects there were no data reported and recorded over medium-term except for placebo. As in the short-term results, nasal stuffiness, hyperthermia and confusion were also only reported in the placebo arms and surprisingly as well for constipation (Table **2**).

In the long-term over half of the patients experienced blurred vision with flupenthixol and over one fifth with fluphenazine. Over a third of the patients experienced constipation with fluphenazine. Dry mouth was seen in over half of the patients with flupenthixol and fluphenazine while it was seen with a third of the patients for pipotiazine depot. The rates of increased salivation and urinary retention for flupenthixol were similar to that of placebo. Again nasal stuffiness, hyperthermia, tachycardia and confusion were reported only in the placebo arm (Table **3**).

DISCUSSION

This is a comprehensive review looking into the anticholinergic side effects of long-acting antipsychotics. The paucity of comparisons between long-acting injectable first- and second-generation antipsychotic agents makes this review useful as this topic has received limited attention in the literature but certainly relevant for the outcome of patients. The study has included all the depot antipsychotic found in Cochrane trials at the time our study was completed.

The data was checked twice to ensure accuracy. All data were collected from the Cochrane reviews which select studies using rigorous criteria to ensure quality. Our study was also inexpensive as all the data was free for us to access online in the Cochrane library. The data was homogenous across the studies. Trials from many different settings and types of care provision are added and is likely that to increase the utility of these findings [4].

However, there were a number of shortcomings. The most important was the general lack of good quality data. There are a number of reasons for this. Many studies have not reported or recorded anticholinergic side effects. With older compounds researchers used higher doses in clinical trials and therefore it is more likely that they show a higher prevalence rate of anticholinergic side effects than newer compounds [8]. Another possible problem was the use of

Table 1. Summary of Short Term Data for Long-acting Injections

	General	Blurred vision	Constipation	Dry mouth	Urinary retention	Nasal stuffiness	Hyperthermia	Increased salivation	Tachycardia	Confusion
Placebo	5.9 (2-19)	2.9 (2-5)	10.4 (8-12)	2.7 (2-4)	4.3 (2-11)	0.0 (0-8)	17.9 (11-28)	7.7 (5-11)	10.5 (7-15)	0.0 (0-13)
Bromperidol depot*		-	0 (0-12)	0 (0-12)	-	-	-	3.7 (1-18)	-	-
Flupenthixol depot*	-	27.4 (18-40)	9.7 (5-20)	-	-	-	-	-	-	-
Fluphenazine depot*	-	24.5 (15-38)	34.3 (21-51)	22 (16-30)	6.1 (2-17)	-	-	-	-	-
Fluspirilene decanoate depot*	-	14.3 (6-31)	40 (20-64)	14.6 (7-27)	2.6 (0-13)	-	-	-	-	-
Methylperidol depot*	-	5.1 (1-17)	2.6 (0-13)	2.6 (0-13)	-	-	-	-	-	-
Pipotiazine palmitate depot*	-	0 (0-23)	-	0 (0-23)	-	-	-	-	-	-
Risperidone depot†	-	-	4.8 (3-7)	28.1 (16-45)	-	-	-	5.7 (4-9)	2 (1-4)	-

Data in Table (**1**) has been adopted from MMedSc dissertation [4]**.** The short term data were also published in Journal of Clinical Psychopharmacology [8]**.**
† New Generation, * Older Generation,- No data reported or recorded

anticholinergic medications. We were not able to control for the use of anticholinergic medications in the trials as they were not detailed enough. The anticholinergic use is significantly lower when patients are treated with second-generation alone as compared with treatment strategies involving the use of high potency first-generation antipsychotics alone or in combination with second-generation antipsychotics [10]. Risperidone is also associated with a more frequent use of anticholinergic drugs than olanzapine [10]. The use of anticholinergic medication is likely to have inflated our data on the incidence rate of anticholinergic side effects. Our finding of double counting was a similar problem to previous findings [8].

A further limitation of this study is its wider applicability in the general population. The data in our study are summary data from many trials and as such they could be considered as a large case series. A design which would give more accurate prevalence data for the population with wider applicability would be a survey. However, doing such a survey would require more resources [8].

Most of our data came from short-term studies, very few from medium-term studies although improving for long-term studies. One of the reasons for the paucity of data is that there are few published trials with depot medications. Another problem is the 5% to 10% cut off the pharmaceutical industry apply for reporting data on side effects. In addition, the medium- and long-term studies have been seldom performed due to the cost implication and high dropout rates associated with these types of studies. A comprehensive review of the literature is likely to make some of the individual data more robust but it is not likely to change our main conclusion given that oral first-generation did not differ from the second-generation in regards of anticholinergic side effects [8].

We found that fluphenazine has the highest incidence of the most common anticholinergic side effects namely blurred vision, constipation and dry mouth over short-term. Similarly, fluphenazine and flupenthixol have significant effect on blurred vision and dry mouth over long-term. Data on depot risperidone is inconclusive. In our data they seem to cause significant dry mouth but for constipation not different to placebo and no data on blurred vision or urinary retention. This is likely to have many more adverse effects than have been reported and are further supported by the pattern of non-reporting.

There are two novel long-acting antipsychotic introduced to the market, namely olanzapine pamoate and paliperidone palmitate. In a review of olanzapine long-acting injections with oral olanzapine and placebo it was conclude that olanzapine injections was well tolerated during short and long-term treatment and it had an adverse event profile consistent with that of the oral formulation, with the exception of adverse events that are related to the intramuscular route of administration and post injection syndrome where a small proportion developed either symptoms of sedation or delirium [11]. In the recent study, published by Ozbilen and Adams [8], for oral olanzapine the prevalence of blurred vision was 12.2% (CI 11 to 14) and for dry mouth it was 21.5% (CI

Table 2. Summary of Medium Term Data for Long-acting Injections

	General	Blurred vision	Constipation	Dry mouth	Urinary retention	Nasal stuffiness	Hyperthermia	Increased salivation	Tachycardia	Confusion
Placebo	-	11.1 (4-25)	0 (0-10)	25 (11-47)	5 (1-24)	10 (2-40)	-	-	-	-
Bromperidol depot*	-	-	-	0 (0-28)	-	-	-	-	-	-
Flupenthixol depot*	-	0 (0-11)	-	-	-	-	-	-	-	-
Fluphenazine depot*	-	16.7 (10-27)	-	4 (1-20)	-	-	-	5.6 (1-26)	-	-
Fluspirilene decanoate depot*	-	0 (0-13)	-	0 (0-13)	-	-	-	-	-	-
Methylperidol depot*	-	-	-	-	-	-	-	-	-	-
Pipotiazine palmitate depot*	-	-	-	-	-	-	-	-	-	-
Risperidone depot†	-	-	-	-	-	-	-	-	-	-

Data in Table (**2**) has been adopted from MMedSc dissertation [4].
† New Generation, * Older Generation,- No data reported or recorded

20 to 23). In a review of paliperidone palmitate the incidence of extrapyramidal symptoms, prolactin elevation, use of anticholinergic medication and weight gain with paliperidone was low. In this review there were not much data on anticholinergic side effect except that one study reported dry mouth to be a common adverse event and constipation to be more common with placebo [12].

Constipation doesn't only constitute discomfort for the patient, but it can also be severe and lead to serious consequences such as paralytic ileus, bowel occlusion and death [13]. In the review of literature, constipation has been shown to be high for second-generation antipsychotics with some variability between individual compounds. Clozapine has the highest constipation related mortality rate. This mortality rate was three times higher than the mortality rate of agranulocytosis [13]. In our study, constipation was over the short-term the most common side effect for fluphenazine depot, fluspirilene decanoate depot and over long-term for fluphenazine depot. The prevalence of constipation was low with risperidone depot.

Adams *et al*. (2001) compared the prevalence/incidence of extrapyramidal symptoms and tardive dyskinesia between first-generation oral and long-acting injections and found that they were similar [14]. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Cost Utility of the Latest Antipsychotics in Schizophrenia Study (CUtlASS) trials, the prevalence of extrapyramidal symptoms did not differ between second-generation antipsychotic and first-generation comparator-perphanazine in CATIE and various first-generations (but predominantly sulpride in CUtlASS) [15, 16]. The CATIE study also presents data on anticholinergic side effects in all three phases of the trials [15, 17, 18]. On all three phases quetiapine was associated with higher anticholinergic side effects than other atypicals and the comparator perphanazine. However, overall there were not much differences between first- and second-generation antipychotics in incidence rate of these side effects.

The interconnected pathophysiology and abdominal obesity, insulin resistance, hypertension, and disturbance in lipid metabolism can result in a co-occurrence of risk factors for cardiovascular disease and diabetes known as metabolic syndrome [19]. The association between metabolic syndrome and individual second-generation antipsychotic is variable with olanzapine and clozapine having the highest rate [20]. However, significant weight gain and increases in plasma lipids have also been reported with first-generation antipsychotics, particularly low potency phenothiazines [19].

There have been also a number of large reviews comparing first- and second-generation antipsychotics. Although some studies suggest that there were substantial differences among both first- and second-generation antipsychotic with regards to their propensity to cause extrapyramidal, metabolic and other adverse effects [21, 22], another study suggest that there is variation within both the first- and second-generation classes with reference to each of these adverse effects, without any categorical separation between these two classes [23]. Because the second-generation antipsychotic drugs differ in many properties, including efficacy, side effects, cost, and pharmacology, they do not form a homogeneous class and neither do first-generation antipsychotic drugs. Improper generalization creates confusion and as a result it has been suggested that the classification might be abandoned [22].

Table 3. Summary of Long Term Data for Long-acting Injections

	General	Blurred vision	Constipation	Dry mouth	Urinary retention	Nasal stuffiness	Hyperthermia	Increased salivation	Tachycardia
Placebo	-	3.2 (2-6)	3 (1-6)	0.8 (0-3)	0.9 (0-3)	-	-	0 (0-12)	-
Bromperidol depot*	26.1 (13-46)	-	-	-	-	-	-	-	-
Flupenthixol depot*	-	52.9 (31-74)	-	64.7 (41-83)	-	-	-	-	-
Fluphenazine depot*	8.3 (2-26)	21.4 (16-28)	40 (22-61)	45.5 (34-57)	15 (5-36)	-	-	0 (0-11)	-
Fluspirilene decanoate depot*	-	-	-	-	-	-	-	-	-
Methylperidol depot*	-	-	-	-	-	-	-	-	-
Pipotiazine palmitate depot*	-	0 (0-20)	-	32.3 (19-50)	-	-	-	-	-
Risperidone depot†	-	-	-	-	-	-	-	-	-

Data in Table (**3**) has been adopted from MMedSc dissertation [4].
† New Generation, * Older Generation,- No data reported or recorded

Although our data is inconclusive with unreported and unrecorded data contributing to a lack of good quality data, our data suggests that long-acting first-generation depot antipsychotics are not much different from long-acting second-generations in their anticholinergic side effect profiles. Although more research is needed to confirm these findings, their use should be informed on patient preference and on individual compounds, rather than choosing between first- or second-generation antipsychotics. With regards to the first episode psychosis we conclude that depot antipsychotics could be considered for patients particularly those who prefer depot antipsychotics, those with poor insight and with a risk of non-concordance. However, the risk/benefit ratio should always be weighed up and discussed with individual patients before any type of antipsychotic of any form (i.e. oral or long-acting injections) is started.

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CONFLICT OF INTEREST

There have been no conflicts of interest or financial interests.

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