Dose equivalents for second generation long-acting injectable antipsychotics: The minimum effective dose method

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ABSTRACT

Background: The concept of dose equivalence of depot medication is important for many scientific and clinical purposes.
Methods: A systematic literature search on four second-generation antipsychotics available as long-acting injectable drugs and haloperidol was conducted. We used the minimum effective dose method which is based on randomized fixed dose studies where the smallest dose which was significantly more efficacious than placebo in the primary outcome was declared as minimum effective dose. We calculated equivalent doses from acute phase studies but we also reported the minimum effective doses found in relapse prevention studies.
Results: The acute phase minimum effective doses/olanzapine equivalents were: aripiprazole lauroxil 441 mg (300 mg aripiprazole)/4wks/0.71; aripiprazole 400 mg/4 weeks/0.95 (aripiprazole maintena); paliperidone palmitate 25 mg/4 weeks/0,06; risperidone 25 mg/2 weeks/0,12; RBP-7000 90 mg/4 weeks/ 0,21; olanzapine 210 mg/2 weeks/1.
Conclusions: The minimum effective dose method is an operationalized and evidence-based approach for determining antipsychotic dose equivalence which can also be applied to long-acting injectable formulations. Doses may not have been chosen low enough to find the truly minimum effective dose. Comparisons with other methods will be necessary to come to ultimate conclusions.

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1. Introduction

Equivalent doses of antipsychotics can be useful for many purposes. Within the clinical situation, it is important to use this method when it becomes necessary to switch one antipsychotic for another or when two drugs need to be combined. Dose equivalence estimates are also needed for the design of fair comparisons in trials or meta-analyses (Heres, 2006; Leucht et al., 2013) or when doses of different antipsychotic drugs need to be converted into 1 unit. Cost calculations and treatment guidelines may also make it necessary to estimate equivalent doses of antipsychotic drugs.

Patel et al. (2013) discussed in a comprehensive review different methods to define dose equivalence: The classical mean dose chlorpromazine equivalent method by Davis, 1974 (Davis, 1974), the dose-response curve method to define near-to-maximum doses by Davis and Chen (2004), methods based on the maximum licensed doses of different antipsychotic drugs (MacE and Taylor, 2005; Milton et al., 1995a), daily defined doses (DDD) of the World Health Organization and Consensus methods (Andreasen et al., 2010; Gardner et al., 2010; Kane et al., 2003b).

As all these methods have advantages and limitations, recent reviews used them on a one by one basis to provide dose equivalencies for second-generation antipsychotics and to compare the findings. (Woods, 2003), (Leucht et al., 2014), (Leucht et al., 2016; Leucht et al., 2015). However, these reviews were restricted to oral forms of administration; long-acting injectable (LAI) "depot" formulations have so far not been addressed. With this current systematic review we tried to fill the gap by deriving dose equivalencies of haloperidol decanoate and all second-generation antipsychotics available as LAI's with the minimum effective dose method first presented by Woods (2003) and later updated by Leucht et al. (2014): paliperidone palmitate, aripiprazole lauroxil®, aripiprazole maintena®, risperidone depot and olanzapine pamoate.

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2. Methods

We included studies on adult patients with schizophrenia or schizoaffective disorder according to DSM-III, DSM-IV, DSM-IV-TR, Feigner Criteria, ICD-9, ICD-10 and the four SGAs available as a long-acting injectable formulation: paliperidone palmitate, aripiprazole depot, risperidone depot, olanzapine pamoate. The aripiprazole drugs "maintena®" (prolonged-release suspension for injection) and "lauroxil" (an extended-release prodrug of aripiprazole for injection) were analysed separately, due to their different release mechanism. The same holds true for paliperidone palmitate one monthly (Xeplion®) and three monthly (Trevicta®), and for Risperidal Consta® (an extended-release microspheres formulation) and RBP-7000 (Reckitt BeckiserPharmaceuticals-7000, a sustained-release formulation of risperidone for monthly subcutaneous injection).

We also included haloperidol decanoate which is the standard first generation antipsychotic drug, which is also available as LAI.

We excluded studies in populations with special considerations such as adolescents, elderly, first-episode patients, treatment resistance patients, patients with predominant negative symptoms and other diagnosis than schizophrenia or schizoaffective disorder. These specific patients were excluded as different dosages might be required for them (currently there are no relevant studies in this area known to the author). An electronic search was conducted with "MEDLINE", "EMBASE", "PsycINFO", "Cochrane Library", "Pubmed". "BIOSIS Citation Index", "Clinicaltrials.gov" and "Platform of the World Health Organisation". For search terms see webappendix 1. The last search was performed in April 2016. We also researched the medical reviews that pharmaceutical companies submitted to the FDA and we inquired with the providers of paliperidone palmitate and risperidone depot (Janssen-Cilag), aripiprazole maintena (Otsuka/Lundbeck), aripiprazole lauroxil (Alkermes), olanzapine pamoate (Lilly) and Indivior PLC (RBP-7000) for literature concerning the aforementioned medications. Data was extracted independently by at least two reviewers (P.H.R., S.L.) and remaining questions were clarified with SH. The analysis was conducted with Excel 2010.

2.1. Minimum effective dose method

We included all available randomized, fixed dose, placebo-controlled studies on the mentioned compounds and followed the approach first presented by Woods (2003) and later refined by Leucht et al. (2014). This means that we identified the lowest fixed dose of the included LAIs that was consistently more efficacious than placebo in the primary outcome in at least one double-blind randomized controlled trial (RCT). As in Woods (2003), but differently to Leucht et al. (2014) we accepted RCTs in which a very low dose of the same drug that was assumed to be ineffective and thus a "pseudo-placebo" by the original authors were also included, because relatively few LAI dose-finding studies are available (e.g. in study Kane et al., 2009) the pseudo-placebo was a subtherapeutical dose of four weekly 45 mg olanzapine pamoate). Statistically significant superiority in one RCT compared to placebo was considered sufficient because due to various problems in trial methodology in recent years, such as increasing placebo response (Kemp et al., 2010; Khin et al., 2011) and high dropout rates (Spineli et al., 2013), it is currently difficult to demonstrate statistical superiority. These developments lead to an increasing number of failed trials (studies in which neither the new drug nor the active comparator was more effective than the placebo), so that even well-established compounds such as olanzapine (Kinon et al., 2011) sometimes do not show separation from the placebo. In this environment, we feel it is unlikely that superiority to the placebo is just a chance finding (Leucht et al., 2014).The primary outcome was the mean change of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) total score or the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) total score from baseline in the intention-to-treat dataset for acute phase

studies and relapse as defined by the individual studies for relapse prevention trials. The derived minimum-effective doses were then used to derive equivalent doses expressed in olanzapine equivalents for every examined drug. Olanzapine was chosen as the primary reference drug because it was also used in our prior publications which should be complemented by the current one (Leucht et al., 2016; Leucht et al., 2015; Leucht et al., 2014). 441 mg/4 weeks, which for the prodrug aripiprazole lauroxil would represent 300mg of aripiprazole. We first used the applied doses and their injection intervals to estimate daily doses for olanzapine pamoate (15 mg/d) and aripiprazole lauroxil (10.7 mg/d, derived from 300 mg/4 weeks aripiprazole which is equivalent to aripirazole lauroxil 441 mg/4 weeks). To obtain 1 mg/d olanzapine equivalents for aripiprazole lauroxil we divided the daily doses (10.7/15) and received an olanzapine equivalent for aripiprazole lauroxil of 0.71 mg/d. Thus 0.71 mg/d of aripiprazole lauroxil is equivalent to 1 mg/d olanzapine pamoate in our case (see Table 2).

Equivalent doses were only calculated based on the acute phase studies. Relapse prevention studies were not used for this purpose, because their primary outcome is different (relapse instead of mean PANSS change) and because theoretically for relapse prevention lower doses might be minimally effective than those for acute treatment. However, we displayed the minimum effective doses for relapse prevention in separate tables, because we felt that this information could be useful for readers. Here, we assumed that if a lower dose was minimally effective in the acute phase studies than in relapse prevention studies, we would have considered such a dose also as the minimum one for relapse prevention. This procedure again took into consideration the relative paucity of available studies.

3. Results

The PRISMA diagram shows the flow of the search (Webappendix 2). A description of the included studies is provided in Webappendix 3. The minimum effective doses and dose equivalents derived from acute phase studies are presented in Tables 1 and 2. Minimum effective doses for relapse prevention are presented in Table 3.

3.1. Acute phase studies

The duration of the 10 acute phase studies ranged between 8 and 13 weeks (median 12) and they had 247–648 participants (median 378). No acute phase study was available for paliperidone palmitate three monthly (PP3M) and haloperidol decanoate.

3.2. Aripiprazole lauroxil

We identified one study for aripiprazole lauroxil (Meltzer et al., 2015) which compared 441 mg/4 weeks (300 mg of aripiprazole) and 882 mg/4 weeks (600 mg of aripiprazole) with placebo. 441 mg/4 weeks was the lowest dose that was significantly superior to the placebo and it thus was defined as the minimum effective dose. The equivalent dose to 1 mg olanzapine was 0.71 mg.

3.3. Ariprazole maintena

Another study compared aripiprazole maintena (Kane et al., 2014) in a dose of 400 mg/4 weeks with placebo, and there was a statistical separation (Kane et al., 2014). The equivalent dose to 1 mg olanzapine was 0.95 mg.

3.4. Olanzapine pamoate

For olanzapine pamoate one placebo-controlled fixed dose acute study with doses between 150 and 405 mg/2 weeks/4 weeks (EliLilly2) was included. 210 mg/2 weeks was the minimum effective dose.

Table 1
Results of placebo-controlled, fixed dose acute phase studies.

	Dose groups mg/4w				
ARIPIPRAZOLE lauroxil (AL)	441 mg AL/ 300 mg ari	882 mg AL/ 600 mg ari			
Meltzer 2015 (Meltzer et al., 2015)	+	+			
ARIPIPRAZOLE maintena	50	300	400		
Kane 2014 (Kane et al., 2014)		a	+		
	Dose groups in mg/2w/4w				
OLANZAPINE PAMOATE	45/4w	150/2w	210/2w	300/2w	405/4w
Lauriello 2008 (Lauriello et al., 2008)			+	+	+
	Dose groups in mg e.q.[b]/4w				
PALIPERIDON PALMITATE	25	50	75	100	150
Pandina 2010 (Pandina et al., 2010)	+			+	+
Nasrallah 2010 (Nasrallah et al., 2010)	+	+		+	
Kramer 2010 (Kramer et al., 2010)		+		+	
Gopal 2010 (Gopal et al., 2010)		–		+	+
Takahashi 2013 (Takahashi et al., 2013)			+		
	Dose groups in mg/biweekly				
RISPERIDONE	25	50	75		
Kane 2003 (Kane et al., 2003a)	+	+	+		
	Dose groups in mg/4w				
RBP–7000	90	120			
Nasser 2016 (Nasser et al., 2016)	+	+			

+ = statistically significantly better than placebo/very low dose in the primary outcome. – = not statistically significantly better than placebo/very low dose in the primary outcome. The light grey background illustrates the minimum effective dose based upon our main (primary) criterion (at least one trial with a statistically significant difference compared to placebo/low-dose).
[a]Aripiprazole lauroxil® and Aripiprazole maintena® are different formulations of the same drug. Due to possible differences concerning the metabolism we present results for both formulations.
[b]In this study a single decrease to aripiprazole 300 mg based on tolerability was permitted, patients could have a have their dose increased back to 400 mg for symptomatic control, if needed.
[c]Presentation in mg e.q. means that 25 mg e.q. = 39 mg/monthly, 50 mg e.q. = 78 mg/monthly, 100 mg e.q. = 156 mg/monthly, 150 mg e.q. = 254 mg/monthly.

3.5. Paliperidone palmitate

For paliperidone palmitate there were 5 placebo-controlled acute studies with doses between 25 and 150 mg/4 weeks (Fu et al., 2015; Gopal et al., 2010; Kramer et al., 2010; Nasrallah et al., 2010; Pandina et al., 2010; Takahashi et al., 2013). 25 mg/4 weeks was found to be significantly superior to the placebo and was considered as the minimum effective dose. The equivalent dose to 1 mg Olanzapine was 0.06 mg.

Table 2
Minimum effective doses and dose equivalents based on the acute phase studies.

Drug	Minimum effective dose mg/w	ARI lau 1 mg	ARI main 1 mg	OLA 1 mg	PAL 1 mg	RIS 1 mg	RBP-7000 1 mg
ARI lau (AL)	441 AL (300 mg ari)/4w	1	0.75	0.71	11.9	5.9	3.3
ARI main	400/4w	1.3	1	0.95	15.89	7.94	4.47
OLA	210/2w	1.4	1.05	1	16.67	8.33	4.69
PAL	25/4w	0.08	0.06	0.06	1	0.5	0.28
RIS	25/2w	0.17	0.13	0.12	2	1	0.56
RBP-7000[a]	90/4w	0.3	0.22	0.21	3.56	1.78	1

We present the minimum effective doses and the doses in mg that are equivalent to 1 mg/d aripiprazole lauroxil (ARI lau), 1 mg/d aripiprazole maintena (ARI main), 1 mg/day olanzapine (OLA), 1 mg/day paliperidone (PAL). Daily doses were calculated referring to 28 d: aripiprazole lauroxil 10,7 mg/d (derived from 300 mg/4 w aripiprazole which is equivalent to aripirazole lauroxil 441 mg/4 w), aripiprazole maintena 14,3 mg/d, olanzapine 15 mg/d, paliperidone 0,9 mg/d, risperidone 1,8 mg/d, RBP-7000 3,2 mg/d.
[a] It has to be stated that the formulation of RBP-7000 was designed to be administered subcutaneously. So different equivalent doses may result for this compound due to different metabolism in comparison to other depot drugs.

3.6. Risperidone Consta®

In one study risperidone Consta® doses between 25 and 75 mg/2-weeks were compared with a placebo (Janssen; Kane et al., 2003a). 25 mg/2 weeks was the minimum effective dose, leading to a 1 mg olanzapine equivalent of 0.12 mg.

3.7. Risperidone RBP-7000

One study compared 90 mg/4 weeks and 120 mg/4 weeks of RBP-7000 to placebo. 90 mg/4 weeks was the minimum effective dose (Nasser et al., 2016) and the dose equivalent to 1 mg olanzapine was 0.2 mg.

3.8. Relapse prevention studies

The 7 included studies had a median duration of 52 weeks (24–64 weeks) and included a median of 334 participants (range 43–1065).

3.9. Aripiprazole

In two studies 400 mg/4 weeks aripiprazole in the abilify formulation were more efficacious than the placebo (Kane et al., 2012) and then a subtherapeutic dose of 50 mg/4 weeks (Fleischhacker et al., 2014) In both studies it was also possible to reduce from 400 mg to 300 mg once during the trial, but as the number of patients using this option was small (7.2% in Fleischhacker et al., 2014 and 3.7% in Kane et al. (2012)), 400 mg/4 weeks were declared as the minimum effective dose for relapse prevention (Fleischhacker et al., 2014; Kane et al., 2012).

Table 3
Minimum effective doses identified in placebo-controlled, fixed dose, relapse prevention studies.

	Dose groups mg/4w				
ARIPIPRAZOLE maintena	50	300	400		
Fleischhacker 2014 (Fleischhacker et al., 2014)	*	[a]	+		
Kane 2012 (Kane et al., 2012)		[a]	+		
	Dose groups in mg/2w/4w				
OLANZAPINE PAMOATE	45/4w	150/2w	210/2w	300/2w	405/4w
Kane 2010 (Kane et al., 2010)	*	+		+	+
PALIPERIDONPALMITATE	25	50	75	100	150
Fu 2015 (Fu et al., 2015)		+	+	+	+
	Dose groups in mg/4w				
HALOPERIDOL	25	50	60	100	200
Eklund 1990 (Eklund and Forsman, 1990)			+		
Kane 2002 (Kane et al., 2002)	*	+		+	+
	Dose groups in mg/12weekly				
PP3M	175	263	350	525	
Berwaerts 2015 (Berwaerts et al., 2015)	+	+	+	+	

+ = statistically significantly better than placebo/very low dose in the primary outcome. − = not statistically significantly better than placebo/very low dose in the primary outcome. The light grey background illustrates the minimum effective dose based upon our main (primary) criterion (at least one trial with a statistically significant difference compared to placebo/low-dose).
[a] In this study a single decrease to aripiprazole 300 mg based on tolerability was permitted, patients could have a have their dose increased back to 400 mg for symptomatic control, if needed.
*These doses were used as "pseudo-placebos" in their studies.

3.10. Haloperidol decanoate

In Eklund et al. (Eklund and Forsman, 1990) 60 mg haloperidol decanoate 4 weekly was significantly superior to the placebo and in Kane et al. (2002) doses of 50, 100 and 200 mg 4 weekly were significantly better than 25 mg 4 weekly. (Kane et al., 2002) We decided that 50 mg haloperidol decanoate 4 weekly is the minimum effective dose.

3.11. Olanzapine pamoate

In Kane et al. fixed doses between 150 mg/2 weeks and 405 mg/4 weeks (Kane et al., 2009) prevented relapses more effectively than a subtherapeutic dose of 45 mg/4 weeks (Kane et al., 2009). Thus, 150 mg/2 weeks was considered as the minimum effective dose.

3.12. Paliperidone palmitate

Fu et al., 2015 (Fu et al., 2015) compared paliperidone 50 mg/4 weeks, 75 mg/4 weeks, 100 mg/4 weeks and 150 mg/4 weeks with placebo and all doses were significantly superior in the prevention of relapses. 50 mg/4 weeks was thus the minimum effective dose.

3.13. Paliperidone palmitate 3-monthly

Berwaerts et al., 2015 (Berwaerts et al., 2015) compared four fixed doses (175–525 mg/12 weeks) of PP3M with placebo for relapse prevention. All doses were efficacious and 175 mg/4 weeks was defined as the minimum effective dose (Berwaerts et al., 2015).

4. Discussion

We used the minimum effective dose method originally presented by Woods (2003) for 4 SGAs (aripiprazole, paliperidone, olanzapine, risperidone) and one FGA (haloperidol) which are available as long-acting injectables in different formulations. Hereby we bridged a gap which grew because prior approaches limited themselves on oral formulations of antipsychotic drugs (Leucht et al., 2016; Leucht et al., 2015; Leucht et al., 2014).

We calculated only dose equivalents from minimum effective doses found in acute phase studies because in previous reviews equivalent doses were also derived from acute phase studies, so comparisons can be drawn easier. We also chose acute phase studies as a reference because in recent literature and clinical practice it is discussed whether long-acting injectables should be administered primarily to acutely ill patients and not secondly after a stabilization phase on oral drugs. This might be useful to prevent destabilization after a switch from oral drugs to long-acting injectables.

The fact that we did not calculate dose equivalents from minimum effective doses in relapse prevention studies may limit our results. Because there were not many randomized fixed dose studies available it is questionable how well the minimum effective doses of the examined drugs could be identified. The value of the minimum effective dose method should be considered in light of the limitations of other methods to define dose equivalence like the classical mean dose method (Leucht et al., 2015), consensus methods (Andreasen et al., 2010; Gardner et al., 2014), Davis' method (Davis, 1974), (Leucht et al., 2013; Leucht et al., 2009), Cochrane meta-analyses (Donnelly et al., 2002; Li et al., 2012; Liu and De Haan, 2009), DDDs (Patel et al., 2013; WHO, 2012), (Leucht et al., 2016) and "maximum licensed methods" (MacE and Taylor, 2005; Milton et al., 1995b), (Committee and Britain, 2012), (Chouinard et al., 1993; Glick and Marder, 2005; Peuskens, 1995).

Future studies should provide dose equivalencies for specific populations. In absence of data for the excluded patient groups it appears safer to recommend the dose equivalencies mainly for chronic patients as they are typical for antipsychotic drug trials in schizophrenia.

A systematic review of various methods to obtain dose equivalents may lead to ultimate conclusions. Further acute phase and relapse prevention studies with broader dose ranges may improve the quality of derived equivalent doses. For this purpose, we examine dose equivalency of depot formulations of antipsychotics by using further methods like the classical mean dose method. Appropriate reviews will be published in the future.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.07.033.

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