Review

A proposal for reducing maximum target doses of drugs for psychosis: Reviewing dose–response literature

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Abstract

Background: Presently, there is limited guidance on the maximal dosing of psychosis drugs that is based on effectiveness rather than safety or toxicity. Current maximum dosing recommendations may far exceed the necessary degree of dopamine D_2 receptor blockade required to treat psychosis. This may lead to excess harm through cognitive impairment and side effects.

Aims: This analysis aimed to establish guidance for prescribers by optimally dosing drugs for psychosis based on efficacy and benefit.

Methods: We used data from two dose–response meta-analyses and reviewed seven of the most prescribed drugs for psychosis in the UK. Where data were not available, we used appropriate comparison techniques based on D_2 receptor occupancy to extrapolate our recommendations.

Results: We found that the likely threshold dose for achieving remission of psychotic symptoms was often significantly below the currently licensed dose for these drugs. We therefore recommend that clinicians are cautious about exceeding our recommended doses. Individual factors, however, should be accounted for. We outline potentially relevant factors including age, ethnicity, sex, smoking status and pharmacogenetics. Additionally, we recommend therapeutic drug monitoring as a tool to determine individual pharmacokinetic variation.

Conclusions: In summary, we propose a new set of maximum target doses for psychosis drugs based on efficacy. Further research through randomised controlled trials should be undertaken to evaluate the effect of reducing doses from current licensing maximums or from doses that are above our recommendations. However, dose reductions should be implemented in a manner that accounts for and reduces the effects of drug withdrawal.

Keywords

Dopamine, antipsychotic, dosing, reduction, maximum

Background

It is widely regarded that the lowest effective dose of drugs for psychosis should be used (National Institute of Clinical and Health Excellence, 2014) to minimise adverse effects, including extrapyramidal (Nyberg et al., 1995; Siafis et al., 2023), cardiac (Girardin et al., 2013), neuroendocrine such as hyperprolactinaemia (Bostwick et al., 2009), and metabolic effects such as weight gain (Wu et al., 2022).

Meta-analyses of dose–response relationships (Leucht et al., 2020; Sabe et al., 2021) suggest that the maximal dosages for drugs for psychosis recommended by their summary of product characteristics (SPC) often exceed the potential therapeutic benefit for most patients. Plateauing clinical response at doses lower than licensed maximums has also been noted for other psychotropics such as serotonin reuptake inhibitors (Furukawa et al., 2019; Johnson et al., 2022).

Clinicians may therefore persevere with agents for longer duration, and at excessively high dosages, than necessary if symptoms have not fully resolved (Mace and Taylor, 2015; Paton et al., 2008). Many clinicians feel that dosages for psychosis drugs should be up-titrated to their licensed maximum before abandoning and switching to an alternative agent. This can result in patients receiving an ineffective treatment for longer, increased side effect burden and delaying the initiation of effective alternatives such as clozapine in treatment-resistant schizophrenia (Howes et al., 2012). This may also result in increased length of hospital admissions, further disrupting patients' lives outside of hospital and leading to worse outcomes.

The British National Formulary (BNF) is used in the UK as a guideline for maximum licensed doses and is frequently used to define high-dose therapy of psychosis drugs (Yorsten and Pinney,

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2000). However, these recommended doses tend to be based on toxicity rather than efficacy data, suggesting that these guideline maximum doses may not lead to any greater therapeutic benefit than lower dosing.

Thioxanthenes such as zuclopenthixol and flupentixol have strong dopaminergic affinity (Nyberg et al., 1995; Taylor, 2009). These are commonly used in UK psychiatric practice; flupentixol and zuclopenthixol are most commonly given through long-acting injectable forms and were, respectively, the most and second-most commonly prescribed long-acting injectable psychosis drugs in the latest analysis (NHS Business Services Authority, 2022).

However, there is minimal available literature comparing these drug's efficacy to placebo. Only two previous trials have been reported for zuclopenthixol (Lacey and Jayaram, 2015), both of which were 40 years ago and demonstrated limitations in their methodology. A similar lack of literature exists for flupentixol, with only one available randomised-controlled trial dating back over 30 years (Shen et al., 2012).

Although dose–response relationships have been explored for the long-acting injectable form of flupentixol (Bailey and Taylor, 2019), the oral form has not been similarly explored. No dose–response studies appear to have been conducted for zuclopenthixol in either form (Coutinho et al., 1999).

High doses of flupentixol decanoate were not found to prevent relapse of mental illness any more effectively than standard doses (Mahapatra et al., 2014). It is also worth noting that the 'high-dose' category of flupentixol decanoate in the review included doses up to 100 mg per week (Cookson, 1987); this is far below the current UK-licensed weekly maximum dose of 400 mg (BNF, 2023a). In addition, studies have found that 40 mg flupentixol decanoate 4-weekly is non-inferior in terms of relapse prevention to fortnightly intervals of the same dose (Taylor, 2009).

Other studies have suggested that patients stabilised on higher doses of flupentixol decanoate were at increased risk of relapse when doses were reduced below 200 mg fortnightly (Cookson, 1987). Prescribers should be cautious about extrapolating this finding to assume that patients cannot reduce doses beyond this point. The methodology employed by this study abruptly halved the participant's depot dose, and rapid reductions in dosing may lead to withdrawal symptoms which may mimic the symptoms of a psychotic relapse (Horowitz et al., 2021).

Data from positron emission tomography (PET) and single-photon emission computed tomography scans show that the dissociation constant (K) for dopamine at D_2 receptors is 1.6 nM and that psychosis drugs with K values higher than 1.6 nM are less likely to produce extra-pyramidal side effects (Seeman and Tallerico, 1999). Literature suggests that a target D_2 occupancy for an agent should not exceed 75%–80% to avoid extrapyramidal side effects (Nord and Farde, 2011; Taylor, 2009). In addition, analysis of one study has found an association between reduced subjective well-being scores and increasing striatal D_2 blockade above 60% with risperidone or olanzapine (Mizrahi et al., 2009). CATIE study data revealed that exceeding 80% D_2 occupancy not only increases the risk of extra-pyramidal side effects but also increases the risk of cognitive impairment (Sakurai et al., 2013). The impact of excessive dopamine concentrations on cognitive functions has been well described previously (Cai and Arnsten, 2019; Goldman-Rakic et al., 2000; Torrisi et al., 2020; Vijayraghavan et al., 2007; Purdon et al., 2003).

Many current maximal licensing doses exceed this threshold of 80% occupancy of D_2 receptors. The plateauing of both receptor occupancy (Lako et al., 2013) and response (Leucht et al., 2020; Sabe et al., 2021) at higher doses suggests that with each dose increase of medication, both the difference in effect at the receptor level and changes in clinical symptomatology would progressively lessen. In addition, maximum doses according to the BNF are often used clinically as comparators to match and switch psychosis drugs with often very different pharmacological profiles.

Flupentixol, zuclopenthixol and haloperidol are strong and selective antagonists at D_2 receptors (Christensen et al., 1984), and their licensed maximum doses correspond to a high proportion of the maximal potential receptor occupancy (see Table 1). Less dopaminergic-focussed medications, such as quetiapine, clozapine and olanzapine, achieve much lower occupancies of D_2 at their maximum licensed doses (Yonemura et al., 1998).

Whilst the effect of psychosis drugs is correlated with the occupancy of D_2 receptors, their receptor binding profiles can differ significantly (McCutcheon et al., 2023). Complete blockade of dopamine receptors cannot explain the full scope of their action (Tost et al., 2010), which is evident from the low affinity that clozapine, arguably the most effective drug in treating psychosis (Wagner et al., 2021), has to D_2 receptors (Lako et al., 2013).

There is increasing research into the role of prefrontal cortex glutamate deficiency in the pathophysiology of schizophrenia (Grunder and Cumming, 2016). N-methyl-D-aspartate receptor antagonism by drugs such as ketamine may lead to both positive and negative psychotic symptoms, as well as cognitive impairment (Kropotov, 2016). In addition, it has been suggested that both agonism of 5-HT_{1A} (Bantick et al., 2001; Ohno, 2011) and inverse agonism of 5-HT_{2A} and 5-HT_{2C} (Sullivan et al., 2015) also have therapeutic effects on negative symptoms and cognitive impairment in schizophrenia.

There is the suggestion that antagonism of the H_1 receptor may also play a role in the beneficial effects of psychosis drugs (Fell et al., 2012; Roegge et al., 2007). However, while some PET imaging studies have investigated H_1 receptor antagonism for antihistamines (Tagawa et al., 2001), there is limited data on H_1 receptor occupancy curves for drugs with high efficacy to histaminergic receptors such as quetiapine (Fischer and Boggs, 2011) and clozapine.

For this review, we have focussed solely on D_2 receptor antagonism due to this being the most widely researched area in developing psychosis. However, it is important to bear in mind the involvement of a wide array of neuroreceptors in causing psychopathology as research into this area develops.

Method

This review aimed to devise suggested maximum target dosages for psychosis drugs based on efficacy rather than toxicity. Analysis was conducted for seven of the most frequently prescribed psychosis drugs in the UK according to the most recent prescription data (NHS Business Services Authority, 2022).

We first derived data from two recent meta-analyses of dose–response relationships (Leucht et al., 2020; Sabe et al., 2021). The dose corresponding to the peak response on dose–response curves was used where a peak was observed. Where dose–response

Table 1. A list of commonly prescribed drugs for psychosis in the UK (NHSBSA, 2022) along with clozapine and their respective maximum licensed doses according to the British National Formulary (BNF).

Drug	BNF maximum dose (mg)	Corresponding D_2 receptor occupancy (%)	Maximal potential D_2 occupancy (V_{max}, %)	D_2 occupancy compared to V_{max}	Dose corresponding to 80% D_2 occupancy (mg)
Amisulpride Lako et al. (2013)	1200	76.3	85.0	0.898	n/a
Aripiprazole Kegeles et al. (2008)	30	95.7	100.3	0.954	5.7[a]
Clozapine Lako et al. (2013)	900	54.2	61.7	0.878	n/a
Flupentixol Reimold et al. (2007)	18	96.4	100.0	0.964	8
Haloperidol Lako et al. (2013)	20	89.0	91.9	0.969	4.37
Olanzapine Lako et al. (2013)	20	72.9	96.5	0.756	31.3
Quetiapine Lako et al. (2013)	800	34.1	49.1	0.695	n/a
Risperidone Lako et al. (2013)	16	86.6	92.4	0.937	6.9
Zuclopenthixol Nyberg et al. (1995)	150	94.5	95.47	0.989	8.27

[a]Aripiprazole works through partial agonism of the D_2 receptor, so this value cannot be used to accurately compare efficacy with psychosis drugs working through full antagonism.

Table 2. Doses in milligrams of various drugs for psychosis correspond to maximally effective doses using data from two dose–response meta-analyses.

Drug	Dose leading to peak response (mg)				Corresponding D_2 occupancy to highest value (%)
	Leucht et al. (2020)	Sabe et al. (2021)		Highest value (mg)	
	Positive Sx	Negative Sx			
Amisulpride	537 (ED_{95})	708.3	675	708.3	71.2
Aripiprazole	15	14.8	16.1	16.1	92.1
Haloperidol	8.1	9.9	8.2	9.9	86.2
Olanzapine	15.2 (ED_{95})	9.52 (ED_{95})	15.5 (ED_{95})	15.5	68.1
Quetiapine IR	297 (ED_{95})	407	267	407	26.3
Quetiapine ER	739 (ED_{95})	774 (ED_{95})	707 (ED_{95})	774	33.8
Risperidone	8.2	10.3	9.7	10.3	83.7

relationships had not yet reached a response peak, the mean dose leading to a 95% reduction in symptoms proportionate to the maximal possible reduction (ED_{95}) (Leucht et al., 2020) was used instead. This does not equate to the dose resulting in 95% of patients experiencing a reduction in their symptoms.

One meta-analysis recommended separate ED_{95} values for positive and negative symptoms (Sabe et al., 2021), whereas the other amalgamated these for a single value (Leucht et al., 2020). The largest of these three maximal values was used for our recommendations, except where this dose exceeded the current licensing maximum dose. Quetiapine analysis was separated by formulation into immediate release (IR) and extended release (ER), due to a disparity in clinical response between the two preparations (Terao et al., 2023).

Dose–response data were unfortunately not available for some psychosis drugs. Therefore, an alternative strategy was to look at D_2 receptor occupancy relative to other drugs in this class. As demonstrated in Table 1, D_2 occupancy and pharmacological profile differ considerably between classes of psychosis drugs at what is currently regarded as equivalent doses. For example, this could be due to histaminergic (Roegge et al., 2007), muscarinic (Kidambi et al., 2023; Marino et al., 1998; Osaka and Kanazawa, 2023) and serotonergic (Bantick et al., 2001; Ohno, 2011; Sullivan et al., 2015) effects. Therefore, using a proportion of maximal receptor occupancy may allow for more equivalent comparisons between different agents.

Results

Initially, the shape of the dose–response curvature was assessed. For the majority of our examined agents, the relationship between dose and response formed an inverted U, with increasing dose leading to a peak in response, before either stagnating or declining in observed benefit. Exceptions to this included olanzapine (Sabe et al., 2021), as well as ER quetiapine and amisulpride within one of the meta-analyses (Leucht et al., 2020).

Table 2 lists the values corresponding to the maximal expected response of six psychosis drugs according to existing dose–response meta-analyses (Leucht et al., 2020; Sabe et al., 2021).

A lack of data was available for thioxanthenes such as flupentixol and zuclopenthixol. The paucity of high-quality research into these agents may explain why their current licensing doses may be much higher than other more recently developed psychosis drugs (Coutinho et al., 1999; Shen et al., 2012). Of the six agents with available dose–response data, haloperidol had the most similar pharmacological profile to thioxanthenes (Cunningham

Table 3. Doses in milligrams of various thioxanthenes correspond to a certain proportion of D_2 occupancy relative to potential V_{max}.

Drug	80% of V_{max} (mg)	85% of V_{max} (mg)	87.5% of V_{max} (mg)	90% of V_{max} (mg)
Flupentixol	2.7	3.9	4.8	6.1
Haloperidol	2.6	3.7	4.6	5.9
Zuclopenthixol	6.4	9.1	11.2	14.4

Calculations were derived using references listed in Table 1 (Kegeles et al., 2008; Nyberg et al., 1995; Reimold et al., 2007).

Table 4. Estimated peak effective doses for flupentixol and zuclopenthixol using dose–response data for haloperidol.

Drug	Maximal potential D_2 occupancy (V_{max}, %)	ED50 value (*K*)	Dose for 86.2% occupancy of D_2 (mg)	Dose for 93.8% of potential V_{max} (mg)
Haloperidol Lako et al. (2013)	91.9	0.65	9.9	9.9
Flupentixol Reimold et al. 2007)	100	0.68	4.3	10.4
Zuclopenthixol Nyberg et al. (1995)	95.47	1.6	14.9	24.4

Table 5. List of recommended maximum target doses for seven commonly prescribed drugs for psychosis in the UK (NHSBSA, 2022).

Drug	Smallest available tablet preparation in the UK (mg)	Current BNF maximum dose (mg) British National Formulary (2023a), (2023b)	Peak effective dose (mg)	Recommended maximum target dose daily (mg)
Amisulpride	50	1200	708.3	750
Aripiprazole	5	30	16.1	20
Flupentixol	0.5	18	10.4	10.5
Haloperidol	0.5	20	9.9	10
Quetiapine				
IR	25	750	407	425
ER	50	800	774	800
Risperidone	0.25	16	10.3	10.5
Zuclopenthixol	2 (although 25 mg preparation is available)	150	24.4	25

Owens, 2012). Table 3 lists varying doses corresponding to proportionate D_2 receptor occupancy to thioxanthene's maximal potential occupancy (V_{max}).

The dose corresponding to the peak expected response for haloperidol (9.9 mg) (Zimbroff et al., 1997) corresponded to a D_2 occupancy of 86.2%, which equates to 93.8% of haloperidol's potential Vmax. Using these two benchmarks from haloperidol, we have estimated the peak effective dose for flupentixol and zuclopenthixol, which is listed in Table 4. The two methods resulted in markedly different doses for expected peak response, but all values were substantially below the current maximum licensed doses of 18 and 150 mg, respectively.

Due to adverse effects such as inducing seizures (Varma et al., 2011), clozapine is one of the only drugs for psychosis that undergoes therapeutic drug monitoring (TDM) routinely in UK clinical settings (Kar et al., 2016). As a result, clozapine is rarely increased to its maximum licensing dose without close observation of plasma levels. Of note, however, is that dosages of around a third of clozapine's current licensing maximum will result in achieving what is considered to be a therapeutic plasma level of 0.35–0.50 mg/L (Chang et al., 1997; Flanagan et al., 2023).

Using our described strategies for determining maximal effective dosing, we conclude that some current maximum licensing doses of drugs for psychosis in the UK may exceed the maximal potential benefit in terms of symptom remission. However, the dose–response relationship for olanzapine did not demonstrate a clear efficacy peak from the doses assessed. In addition, olanzapine at doses above the current licensing maximum has demonstrated potential use in treatment-resistant psychosis (Bishara et al., 2013; Gannon et al., 2023). A lower maximum dosage for olanzapine cannot therefore be proposed.

New recommended maximum target doses for seven commonly prescribed psychosis drugs based on the peak effective dose established through this study are presented in Table 5. Values have been rounded up to the smallest available medicinal form for each drug.

Thioxanthenes are most frequently given in long-acting injectable form. It is suggested that for equivalency between oral and depot dosing for both flupentixol (Greenhalgh, 2020) and zuclopenthixol decanoate (Lundbeck, 2022), the oral daily dose should be multiplied by 4 to determine the weekly dose of decanoate long-acting injections. For example, 5 mg oral daily would equate to a 20 mg weekly depot dose. For our recommendations, this would equate to maximum recommended doses of 100 mg/week zuclopenthixol decanoate or 40 mg/week flupentixol decanoate. However, it is noted that previous dose–response

studies for flupentixol decanoate suggest that doses above 40 mg/fortnight may not result in any additional benefit seen (Bailey and Taylor, 2019).

Discussion

Interpersonal variation from demographic factors

These recommended maximums, as in current clinical practice, should not be considered absolute. Many demographics alter the metabolism of psychosis drugs and therefore their effectiveness (Flanagan et al., 2023). These factors include, but are not limited to, age, sex, ethnicity, smoking status and pharmacogenetics (PGx) (Pouget et al., 2014; Wannasuphoprasit et al., 2021).

A reduction in available striatal dopamine receptors has been observed as people age (Mamo, 2015). While the dose required for adequate treatment tends to remain static between the third and fifth decades of life, this then reduces as patients age beyond 50 years (Uchida et al., 2008). Our recommended maximums may therefore still be too high for elderly patients. A guide could be for elderly patients to have maximum doses of a quarter to a half of the proposed adult dose (BNF, 2023a, 2023b). There appears limited evidence-based guidance or recommendations around dosing for adolescents, and this requires further assessment.

In addition, lower dosages may be required for females due to slower drug absorption, metabolism and excretion (Brand et al., 2021). This sex difference appears to be most prominent for olanzapine but is also significantly observed in amisulpride, risperidone and clozapine (Anderson et al., 2015). Although neither meta-analysis has reported the proportion split in sex difference, it is known that males are often over-represented in psychosis studies (Brand et al., 2021). Therefore, gender should be another important consideration for the clinical implementation of our recommended dosages.

Ethnicity can also have a significant effect on dosing, and the proportion of different ethnicities included in these meta-analyses has not been reported. Required clozapine doses for Asian patients may be around 40% lower than African-Caribbean peers, and 20% lower than White counterparts (Flanagan et al., 2023). However, it is also unclear whether ethnicity would have the same impact on other psychosis drugs as it does on clozapine. Real-world studies suggest that there is no significant difference in required doses between varying ethnicities (Maestri et al., 2021) but plasma level differences with ethnicity should be an area of further exploration.

Cigarette smoke is known to induce *CYP450* enzymes, especially *CYP1A2* (de Leon, 2004). This enzyme induction can lead to faster metabolism of clozapine, olanzapine and haloperidol (Ghodke-Puranik and Lamba, 2017). This phenomenon is well reported for clozapine due to the risks of exceeding the therapeutic window if a patient stops smoking (Flanagan et al., 2023). However, the effect that smoking may have on olanzapine and haloperidol may be less frequently accounted for by clinicians. Doses for non-smokers may need to be between 25% and 40% lower than for smokers (de Leon, 2004; Shimoda et al., 1999), and again, this could have implications for our recommended values and would require further study.

Pharmacogenetic implications on dosing

CYP2D6 enzymes are involved in the metabolism of most psychosis drugs, and plasma levels are influenced by variations in the *CYP2D6* gene; this can lead to abnormal metaboliser status, ranging from ultra-rapid to poor metaboliser status (Arranz et al., 2021). Pharmacogenetic-guided dosing recommendations, based on the *CYP2D6* genotype, exist for some psychosis drugs. These recommendations suggest tailoring doses to individual *CYP2D6* genotypes, aiming to simultaneously achieve adequate therapeutic response and tolerability (PharmGKB, 2022).

At present, four psychosis drugs (aripiprazole, risperidone, zuclopenthixol and haloperidol) have PGx dosing recommendations based on *CYP2D6* genotype and subsequent *CYP2D6* metaboliser status (PharmGKB, 2022). For poor and intermediate metabolisers, there are recommendations for lower doses, including zuclopenthixol. For ultra-rapid metabolisers, a dose increase is recommended for haloperidol and zuclopenthixol but only in the case of limited clinical effect. For risperidone, it is recommended for ultra-rapid metabolisers that clinicians consider an alternative drug to treat psychosis (Beunk et al., 2023).

Studies have demonstrated that *CYP2D6* can predict plasma levels for psychosis drugs; *CYP2D6* genetic variability has been found to significantly influence plasma levels of aripiprazole and risperidone (Milosavljevic et al., 2021). In one study (Jukic et al., 2019), through a trial-and-error approach based on prescriber clinical judgement of adjusting doses of aripiprazole and risperidone, poor metabolisers were found to be on significantly lower doses, while ultra-rapid metabolisers were typically prescribed higher doses. For risperidone, it was observed that variability in drug plasma level, driven by *CYP2D6* gene variation, had a significant effect on the therapeutic failure to the drug.

Adopting PGx testing may reduce reliance upon trial-and-error approaches to prescribing. By accounting for metaboliser status, the choice and dose of the drug can be tailored to individuals. Recent guidance for the use of PGx testing in psychiatry suggests that this could be considered following two ineffective treatments (van Westrhenen et al., 2021). A more pre-emptive model of PGx testing would involve utilising PGx testing prior to the initiation of any psychosis drug, and the barriers and facilitators to the implementation of this have recently been reviewed (Jameson et al., 2021).

Therapeutic drug monitoring

Rapid metabolism may therefore warrant treatment above the recommended maximums (Fernandez-Miranda et al., 2020). Combining a PGx approach with TDM could offer a safe and effective way to initiate and monitor response by determining how the prescribed dose corresponds to plasma concentrations (Hiemke et al., 2011; Law et al., 2015; McCutcheon et al., 2018). Blood sampling may indicate if the lack of clinical response is due to excessive metabolism, which would warrant a dosage increase or a switch in the drug. As previously discussed, clozapine assays are regularly obtained in clinical practice for tailoring dose to patient needs, and there are now recommendations for similar drug monitoring to take place for olanzapine if patients are found to be resistant to treatment (Taylor et al., 2021).

At present, TDM is rarely employed for most psychotropic medications, likely due to limited availability of testing facilities, cost of testing and the requirement for phlebotomy (Law et al., 2015). However, almost half of the respondents in a survey of consultant psychiatrists believed that TDM was cost-inefficient (Law et al., 2015). In addition, one in four expressed a belief that plasma concentrations were 'not relevant for drug action in the brain'.

It is true that there are many barriers to TDM at present but plasma levels allow accurate determination of individual pharmacokinetics for specific drugs to accurately tailor dosing. It is not known to what extent accounting for the above demographic factors when making prescribing decisions would eliminate this margin for error.

Thioxanthenes

As expected, the greatest reductions from the current maximum licensed doses we have suggested are for older first-generation agents for which there is little to no available dose–response literature. This is especially the case for zuclopenthixol, which currently has a licensed maximum daily dose of 150 mg per day (BNF, 2023b). Dose-equivalency studies have compared thioxanthene dosing to other psychosis drugs based on various methods (Gardner et al., 2010; Leucht et al., 2014). However, it appears that many of these methods rely on SPC information (Leucht et al., 2014) or expert consensus (Gardner et al., 2010) in the absence of appropriate trial data. This methodology may have led to higher maximum dosing for zuclopenthixol than when accounting for the higher D_2 receptor affinity of zuclopenthixol (Nyberg et al., 1995).

It should also be noted that dose-occupancy curves suggest effective D_2 blockade to occur at doses lower even than those that we have suggested. Doses as low as 6 mg flupentixol (Reimold et al., 2007) and 5 mg zuclopenthixol (Nyberg et al., 1995) result in 70% occupancy of D_2 receptors. Meta-analyses suggest that efficacy appears to not only plateau but sometimes decrease with increasing doses; this has been observed especially with aripiprazole, haloperidol and risperidone (Leucht et al., 2020). This further demonstrates the need for more accurate dosing of patients rather than relying on the maximum licensing dosages.

Limitations

It is important to note the limitations associated with the methodology used to derive these alternative maximum target doses. Mainly, the results for many of the drugs assessed are in fact based on data from a single trial, such as is the case for haloperidol (Leucht et al., 2020; Sabe et al., 2021), or extrapolated from a different, albeit pharmacologically similar, drug such as for zuclopenthixol and flupentixol. In addition, statistical analysis shows great heterogeneity in a number of the drug dose–response curves (Leucht et al., 2020; Sabe et al., 2021), which may weaken the validity of our recommendations.

Ultimately, our recommended maximum doses based on clinical efficacy mirror previous studies on amisulpride (Sparshatt et al., 2009). However, the maximum target dose for quetiapine may still be lower than what we have proposed (Sparshatt et al., 2008), and it is evident that drug formulation significantly affects this (Terao et al., 2023). The response should therefore be analysed on individual bases where possible, and further dose–response analysis should be undertaken, especially for thioxanthene medications if they are to remain in prescribing formularies in the future.

In addition, whilst most individual drug dose–response curves reach a peak before then decreasing, the overall massed curve suggests that potential benefit continues to increase with higher doses when drugs are grouped as one using equivalency data (Leucht et al., 2020), albeit at a much-reduced rate beyond doses of 4 mg risperidone equivalent. It is worth noting that the best method for determining equivalency is still contested, with various methodologies proposed (Gardner et al., 2010; Leucht et al., 2014; Taylor et al., 2021). This is further complicated when comparing drugs of differing pharmacodynamic profiles (Taylor et al., 2021).

Recommended further research

This analysis is based on dose–response data currently available for psychosis drugs. However, as outlined above, this is limited for many medications. The authors would therefore call for further dose–response trials to be conducted to expand the evidence base for high-dose treatment. In addition, randomised-controlled trials should be arranged with participants taking doses of medication greater than our recommended doses to assess the effect of reducing the dosage to our recommendations. It is vital that this reduction takes place in a steady and hyperbolic manner to avoid withdrawal symptoms as a confounding effect (Horowitz et al., 2021; O'Neill et al., 2023).

Conclusion

In conclusion, persistence with medication at excessive doses increases side-effect burden, can delay switching to more effective treatment, and would generally lead to worse outcomes for patients. Clinicians should therefore consider either switching to an alternative agent once our recommended maximal effective doses are reached, or consider TDM and PGx investigations which may provide a rationale for increasing doses above our recommendations.

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Author contributions

JRO – literature compilation, initial draft, data calculation and article revision. AJ – literature compilation, initial draft and article revision. SLM – literature compilation, initial draft and article revision. MD – literature compilation, critical appraisal and article revision. AGC – critical appraisal and article revision. CL – critical appraisal and article revision.

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Ethics and patient consent

This review article did not involve the generation of original participant data and analysed existing publicly available literature. As a result, Ethical Committee approval was not required.

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