

How to classify antipsychotics: time to ditch dichotomies?

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Abstract

The dichotomies of 'typical/atypical', or 'first/second generation', have been employed for several decades to classify antipsychotic but justification for their use is not clear. In the current analysis we argue that this classification is flawed from both clinical and pharmacological perspectives. We then consider what approach should ideally be employed in both clinical and research settings.

Introduction

Over twenty antipsychotics are licensed for the treatment of schizophrenia. Given this number, a classification system is a potentially useful heuristic for both clinician and researcher. In the last three decades the predominant classification of antipsychotic drugs has been in to 'atypical' and 'typical' groupings. More recently the terms 'first', and 'second generation' have been used (Fig 1a), but in practice this is used as a synonym for the atypical/ typical classification. An ideal classification system should map to the pharmacological and/or clinical effects of the drugs and it is not clear that this approach achieves this. More recently a more pharmacologically precise approach, 'Neuroscience Based Nomenclature', has been proposed but is yet to be widely adopted (Fig 1a). In the current paper we discuss the typical/ atypical classification criteria, the evidence supporting their use, and drawbacks of the classification before discussing alternatives.

What is Atypicality?

The term "atypical" was first used in 1975 to describe antipsychotic medications such as clozapine, thioridazine, and sulpride that were observed to induce catalepsy in rats to a lesser degree than "typical" antipsychotics, such as haloperidol and chlorpromazine.¹ A formal definition, however, was not elaborated until the 1990s with a review by Kinon and Lieberman, "Defining Criteria for an Atypical Antipsychotic Drug", where three criteria were specified as: (i) a lack of extrapyramidal side effects (EPSEs) and tardive dyskinesia; (ii) increased therapeutic efficacy; (iii) minimal elevation of prolactin levels.²

There was not, however, an attempt by the field to systematically categorise antipsychotic drugs according to these criteria. Apart from clozapine, drugs developed prior to the approval of risperidone in 1993 were generally understood to show 'typical' properties, while those developed subsequently came under the 'atypical' umbrella. Figure 1b shows this classification against meta-analytic estimates of efficacy and side effect burden for current antipsychotics. This illustrates that 'atypical' drugs are somewhat more likely to have a lower propensity for inducing EPSEs and hyperprolactinaemia than the 'typical' counterparts. However, the boundary is not clear cut, with considerable overlap between groups across criteria. For example, some atypical drugs such as risperidone/paliperidone appear more likely to induce hyperprolactinaemia than several 'typical' drugs such as pimozide or haloperidol. Similarly several atypical drugs such as cariprazine and molindone, are more likely to cause EPSEs than typical drugs such as chlorpromazine and thioridazine.³ Moreover, there is no distinction in efficacy between the two categories. Even the archetypal

antipsychotic, clozapine, while on average more effective than other antipsychotics, does not clearly separate in terms of efficacy from all typical drugs.^{3,4}

Is the situation even less clear cut? The limitations of side-effect comparisons

While the above demonstrates some shortcomings of the typical/atypical classification there does still appear to be, on average, a greater propensity for EPSEs and hyperprolactinaemia to occur following treatment with 'typical' compared to 'atypical' antipsychotics. However, even this difference is likely exaggerated due to the nature of the trials that the meta-analytic estimates of side effect burden are based on.

Antipsychotics antagonise dopamine D2 receptors across the striatum,⁵ including regions critical to normal movement, and it is therefore understandable that D2 blockade can also lead to EPSEs. Positron emission tomography (PET) studies have shown that EPSEs are related to D2R occupancy, and the risk is greatest when occupancy of dopamine receptors by dopamine antagonists exceeds ~85%.^{6,7}

Receptor occupancy is related to dose and therefore, as expected, higher doses are associated with a greater risk of EPSEs.⁸ PET studies indicated that the doses of 'typical' antipsychotics used in many clinical trials, particularly the older ones, would be expected to result in D2R occupancy >85%, whereas the doses of 'atypical' antipsychotics used in clinical trials tend to be associated with D2R occupancy below 85%.⁹ This difference in D2R occupancy is likely to account for some of the higher rates of EPSEs seen in older trials of 'typical' agents. Even in head-to-head trials between 'atypical' and 'typical' drugs the doses of the 'typical' agents have frequently been associated with markedly higher D2R occupancy. For example, an important early trial of olanzapine used olanzapine doses in the range of 5-15 mg OD compared with a haloperidol comparator arm of 15 mg OD.¹⁰ A dose of 15 mg olanzapine has been shown to be associated with around 70% occupancy of striatal D2 receptors.¹¹ The dose of haloperidol required for similar occupancy is around 2.5mg, with doses above 5mg approaching 90% occupancy.^{6,12} It is therefore unsurprising that EPSEs would occur with greater frequency in the haloperidol arm as receptor occupancies would be expected to be markedly higher. When between class comparisons have been restricted to trials that have used doses of 'typical' antipsychotics expected to give similar rates of D2R occupancy to the 'atypical' dose, rates of EPSEs between classes are similar.¹³ Moreover, doses of atypical antipsychotics that would be expected to result in D2R occupancy >85% are associated with higher rates of EPSE.¹⁴ Therefore, much of the difference observed in EPSEs between 'typical' and 'atypical' drugs may be an artefact of dosing differences leading to differences in receptor occupancy.

Hyperprolactinaemia also results from dopaminergic antagonism, and therefore the arguments made above for EPSE also apply to prolactin effects.¹⁵ A mechanistic distinction between EPSEs and hyperprolactinaemia is that in the latter the side effect arises from antagonism at the pituitary, which unlike the striatum, is located outside of the blood brain barrier. This means that drugs with poor penetrance of the barrier are more likely to induce hyperprolactinaemia.¹⁶ There is no evidence, however, for a distinction in blood brain barrier penetration along typical-atypical lines.¹⁷

It is more difficult to obtain drug specific risks of tardive dyskinesia as clinical trials are often of insufficient duration to observe its emergence. Meta-analysis of relevant clinical trial data does, however, suggest that the risk may be higher following long-term treatment with 'typical' as opposed to 'atypical' antipsychotics.¹⁸ In this case the differences do not appear to be driven by dosing differences.¹⁸ The limited number of studies that are available, however make it difficult to determine if this is truly a class effect, for example when individual compounds were examined there was no evidence that quetiapine, paliperidone, or ziprasidone had a reduced propensity for inducing tardive dyskinesia. When specific pharmacodynamic factors are considered it appears that D2 affinity rather than 'atypicality' may be the factor of interest.¹⁹

While not a component of the original criteria for 'atypicality', metabolic side effects have increasingly been associated with atypical antipsychotics. Again, however, when the evidence is examined, it does not divide neatly along class lines. Several 'atypical' antipsychotics such as lurasidone, ziprasidone, and molindone show less propensity to induce weight gain than 'typical' antipsychotics such as chlorpromazine and thioridazine (Figure 1c).

Efficacy

'Atypical' antipsychotics were proposed to not only possess a more benign side effect profile, but furthermore display greater efficacy. Initial trials supported this stance but as evidence accumulated the proposed benefit appeared less clear.^{3,20,21} A major blow to the hypothesis were the findings of the National Institute of Mental Health (NIMH) funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).²² In its first phase CATIE randomised over a thousand patients to either a 'typical' antipsychotic, perphenazine, or one of four 'atypical' drugs (olanzapine, risperidone, quetiapine, or ziprasidone). Participants randomised to the 'typical' treatment were no more likely to discontinue their medication due to a lack of effectiveness than those randomised to one of the 'atypicals'. Two European studies had a similar rationale, the Cost Utility of the Latest Antipsychotic Drugs in

Schizophrenia Study (CUtLASS 1, N=227) trial provided similar findings to CATIE,²³ but the European First Episode Schizophrenia Trial (EUFEST, N=500) did find that haloperidol was associated with a greater risk of all cause discontinuation than several 'atypical' antipsychotics.²⁴ Later meta-analyses have confirmed that there is no clear distinction in efficacy along typical/atypical group lines.³

Similarly, early trials suggested that not only were the 'atypical' compounds advantageous in terms of psychotic symptoms, but that these also showed a benefit in treating cognitive symptoms, a crucial domain given no existing treatments appeared to show significant benefits here.²⁵ Again CATIE produced findings in contradiction of this hypothesis, with individuals on the 'typical' treatment showing the greatest improvement in neurocognitive outcomes,²⁶ and network meta-analyses do not show any clear pattern of superiority for 'atypical' over 'typical'.²⁷

Pharmacology

The criteria proposed to distinguish 'typical' and 'atypical' drugs solely reflect clinical considerations but a distinction in pharmacodynamic mechanisms is implicit, and led to considerable efforts to investigate proposed underlying mechanisms.²⁸ We have demonstrated that the typical/atypical divide does not accurately separate drugs in terms of clinical effects but there may be a value to its continued employment if it summarises fundamental pharmacological difference between the two groups.

Trials of clozapine in the 1980s demonstrated the drug's properties of both improving symptoms in patients where other drugs had failed, and having a low risk of hyperprolactinaemia and movement side effects. This motivated efforts to develop compounds that shared clozapine's pharmacological features in the hope they would also share its clinical profile. While antagonism of the dopamine D2 receptor had already been established as central to antipsychotic efficacy, the effects of clozapine implied the existence of additional mechanisms suitable for therapeutic exploitation.

High affinity for the serotonin (5HT) 2A receptor relative to the affinity for the D2 receptor was proposed as a key factor underlying 'atypicality'.²⁹ Fig 1c summarises the ratio of D2 to 5HT2A affinities across the atypical/typical divide. This shows that, while the D2/5HT2a ratio separates a number of atypical and typical drugs, there are some notable exceptions. In particular, the D2/5HT2a ratios of amisulpride, lurasidone and molindone overlap with those seen amongst typicals, whilst they would put thioridazine and chlorpromazine amongst the

atypicals. Similarly, brexpiprazole fits with the atypical pattern of low D2/5HT2a ratio whilst cariprazine fits the typical pattern. Thus, the groupings do not reflect D2/5HT2a ratios.

Although some separation exists between 'typical' and 'atypical' compounds based on D2/5HT2A ratio, it is unclear as to why this mechanism should be afforded priority over others, given its clinical relevance is unclear. That the ratio is unlikely to be central to efficacy is indicated by the fact that most efficacious non-clozapine antipsychotic is amisulpride,³ a drug that possesses negligible affinity for the 5HT2A receptor. It is also clear that other receptor systems play more important roles in determining side effect burden, such as the histamine H1 receptor for weight gain.³⁰ An alternative approach to selectively focusing on specific receptors is to examine the full receptor profile of each drug in an unbiased data-driven fashion. Using this method it is apparent that the atypical/typical divide captures only a minimum of pharmacological differences at best.³¹

Other mechanisms proposed to underlie 'atypicality', include 'fast dissociation' of drugs from the D2 receptor. The affinity of an antipsychotic (i.e. the K_i) is determined by the rate at which the drug binds to (k_{on}) and the rate at which it dissociates off (k_{off}) the receptor. In practice, however, k_{on} hardly varies between antipsychotics which means the dissociation rate is a proxy for affinity, with compounds displaying fast dissociation possessing a low affinity.³² From figure 1c we can see how an archetypal 'atypical' compound, risperidone, shows greater affinity (and thereby slower dissociation) for the D2 receptor than typical compounds such as sulpiride and thioridazine. While k_{off} may well be an important mediator of clinical effects it varies gradually across compounds (figure 1c) and it is therefore hard to see how it could be used to delineate a dichotomy.

In summary, the typical/atypical dichotomy was built upon a presupposition that the antipsychotics that came to market in the years following the FDA approval of risperidone differed from earlier medications in terms of side-effects, and clinical efficacy. However, it has subsequently become clear that observed differences in side effect profile primarily reflected differences in dosing, and that efficacy differences do not separate with categorical boundaries. This is neatly illustrated by the fact that the original antipsychotic, chlorpromazine, an archetypal 'typical' drug, is highly similar to one of the most recently approved antipsychotics, lurasidone, on all the Kinon and Lieberman criteria and as regards D2:5HT2A ratio (Fig 1). The fact that these two compounds are more similar to each other than to other compounds within their 'class' shows how the classification could lead to false distinctions in a research setting. It also shows that it is not helpful in a clinical setting as a clinician may consider they are making a marked switch in treatment strategy when in fact they are changing to a drug with similar side effect and efficacy profile.

Alternative Classification Schemes

Broad classification schemes such as the World Health Organisation's Anatomical Therapeutic Chemical (ATC) classification system primarily classify medications on basis of clinical indication, with more fine-grained categorisation based on chemical structure. While broad categories are useful for facilitating epidemiological monitoring of drug use, the system is not suitable for clinical use given the chemically based subgrouping are distinct from clinical effects and unfamiliar to clinicians.

An extension of the typical/atypical classification that has seen widespread adoption in both research and clinical settings is the addition of an extra grouping of 'third generation' drugs, namely aripiprazole, cariprazine and brexpiprazole. This grouping appears justified in that compounds share a common pharmacological mechanism (partial agonism of the dopamine D2 receptor) and a similar clinical profile.³ This common property accounts for the fact that these drugs are not associated with raised prolactin concentrations, and can even be used as augmentation agents to reduce prolactin levels in cases of dopamine antagonism associated hyperprolactinaemia, presumably because the D2 partial agonism counters the D2 antagonist's effects on D2 receptors in the pituitary.³³ D2 partial agonism is also thought to account for the fact that rates of extrapyramidal side-effects are much lower than would be expected given the high striatal D2 receptor occupancy levels (generally above 80%) seen at clinical doses with these drugs.³⁴ This does not, however, address the issues outlined above that still pertain to most antipsychotics in the typical/atypical groupings. Moreover, inventing the term 'third generation' to categorise them rarefies the typical/atypical categorisation and also suggests a linear evolution in the development of antipsychotics whereas, in fact, aripiprazole was developed before a number of drugs usually included in the second-generation category.

The Neuroscience Based Nomenclature (NBN) was developed to address the fact that indication-based classification systems do not reflect the underlying pharmacology, often have little bearing on clinical effects, and that existing schemes such as typical/atypical have the flaws outlined above.³⁵ In many respects this is an advance on the typical/atypical scheme in that there is an attempt made to reflect pharmacology in the scheme, although it has not seen widespread uptake yet (fig 1a). A potential drawback of the NBN scheme is, however, that it selects certain aspects of the pharmacology over others based on expert consensus that these aspects are central to the actions of the drugs and uses these to make categories. For example while dopaminergic, serotonergic, and adrenergic mechanisms are used in the scheme, histaminergic affinities do not play a role. This is

despite the fact that antagonism of the histamine H1 receptor is central to the sedative and weight gain properties of a number of psychotropics.³⁰

An alternative to an expert consensus approach is to use a data-driven approach. This was recently applied to classify antipsychotics on the basis of their receptor affinity profile,³¹ using a multivariate approach to identify clusters of drugs with similar receptor profiles. This identified four clusters, one with high affinity for muscarinic receptors (e.g. olanzapine and quetiapine), one with relatively low antagonism of the dopamine D2 receptor (e.g. the partial agonists and lurasidone), one with serotonergic antagonisms (e.g. risperidone), and one with relatively pure dopaminergic antagonism (e.g. amisulpride). These clusters also mapped to side effect profiles with greater accuracy than the approaches we have discussed above. A drawback of a data-driven approach, however, is that all receptors are assigned an equal level of importance regardless of their magnitude of impact in mediating clinically relevant effects.

Drugs that are primarily muscarinic receptor agonists or trace amine-associated receptor 1 (TAAR1) agonists have recently shown efficacy in large clinical studies, and these appear distinct from existing antipsychotics because they do not block D2 receptors and show different side-effect profiles.^{36,37} While novel mechanisms of action have the potential to advance the treatment of psychotic disorders, care must be taken when considering how to categorise these compounds. The role of market incentives in shaping language should not be underestimated. It is likely that this played a significant role in cementing the current typical/atypical dichotomy, and any novel categorisation should not be guided by a desire to promote novel compounds over their off-patent competitors. If these new agents become approved, it could be that a single category of 'dopamine receptor blocker' subsumes the typical/atypical dichotomy to distinguish current drugs from new entrants. However, while pharmacologically accurate, this would obscure important pharmacological and clinical differences between existing compounds, which could be detrimental to patient care. Moreover, the mechanism underlying the action of any new drug would need to be established in clinical studies before a new classification could be justified. For these reasons, we caution against a rush to new categorisations if novel drug are approved and suggest it is preferable to keep the pharmacologically based categories described above until there is sufficient understanding of the clinical pharmacology of new drugs.

Fundamentally any form of classification is a form of dimensionality reduction and so entails a loss of information. The loss of precision inherent when using groupings must be compensated for adequately in terms of any gains obtained in terms of heuristic value. An alternative to groupings is to treat each compound individually. This approach means each drug would be considered in terms of its unique pharmacology. We argue that this is

preferable to the typical/ atypical classification because of the flaws with both the principles and practical application of the latter. However, considering each drug separately has limitations. For example, if researchers wish to investigate common underlying mechanisms they need groupings, and busy clinicians may find it challenging when faced with making rapid treatment recommendations with over twenty drugs and no schema to help guide the process. However, new digitally aided approaches can facilitate what would otherwise be an infeasible task in clinical practice. For example, a tool has been developed without the need for a classification scheme that allows antipsychotics to be ranked by patients and clinicians on the basis of multiple side effect preferences to aid decision making.³⁸

In terms of clinical guidelines, our review of the efficacy and side-effect data makes it clear that there is minimal benefit to using the 'typical'/'atypical' groupings and, if compounds are to be specified, these should be individually described. When it comes to research it is possible to use bespoke groupings that better address the research question. For example, if the hypothesis is that D2/5HT2a ratio is critical for clinical efficacy, then it is most logical to make groupings explicitly along these lines. Likewise, if the question is whether affinity for histamine 1 receptors underlies weight gain, then grouping based on H1 affinity is a better way to test this.

Conclusion

The classification of antipsychotics into two categories of 'typical' and 'atypical', has been the dominant taxonomic approach for over thirty years. Over this period increasing evidence has accumulated that the category is fundamentally flawed in conception and application. As a result, the dichotomy now serves more to obscure than illuminate differences between compounds and we recommend it is no longer used. Alternatives include NbN or data driven approaches. These have the advantage over the typical/atypical classification of not being based on flawed criteria that are not applied consistently in practice. Nevertheless, classification inevitably involves some loss of information that may in some circumstances outweigh its benefits, and different classifications may be more or less appropriate depending on the issue at hand. We recommend researchers and clinicians consider whether a given system is fit for their specific purpose, and whether to use one at all.

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Declaration of Interests

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Author Contributions

RAM, AC, SP, and ODH all wrote the manuscript and approved the final version

Data Availability/Code/Research Material: N/A

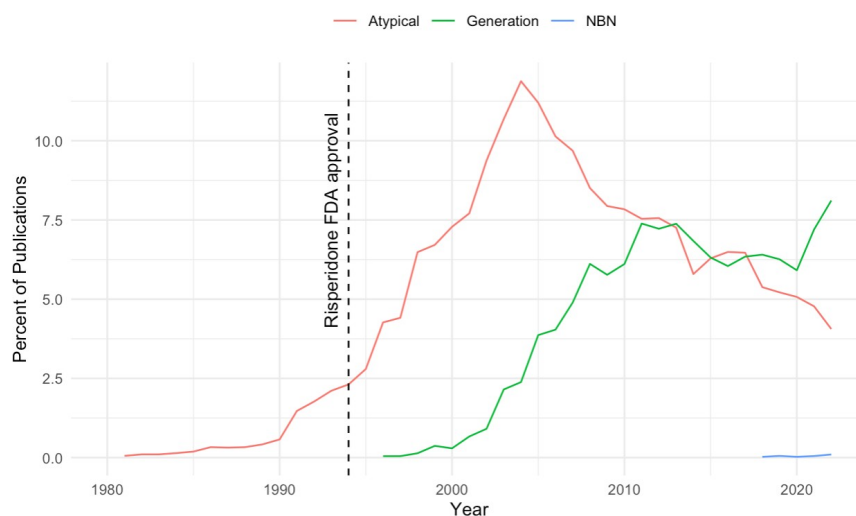
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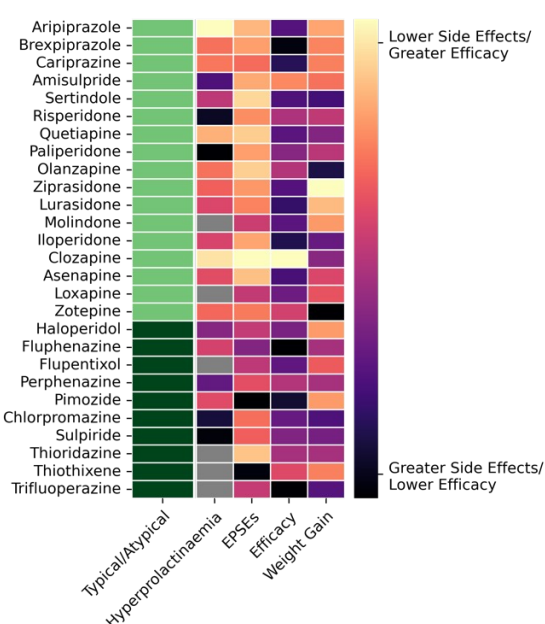
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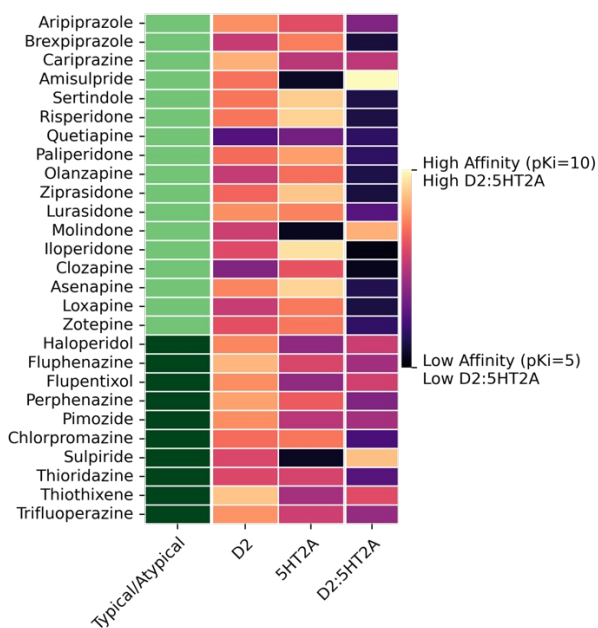


Figure 1. Quantifying Atypicality

A) Trends in nomenclature To quantify the use of the “atypical” terminology we searched PubMed using the search term “atypical antipsychotic” to demonstrate what percent of publications using the word “antipsychotic” have employed this method of classification. We also did the same for “generation antipsychotic”. We then searched for citations of the first paper describing and recommending the pharmacology-based Neuroscience Based Nomenclature.³⁵ The figure shows that the use of the typical/atypical classification remains frequent, and, although it has declined, it has been replaced by ‘first/second generation’ terminology, which essentially duplicates it.

B) Atypicality, efficacy, and side effects The green bar on the left shows antipsychotics grouped into typical (dark green) and atypical (light green), as defined in clinical guidelines, or on basis of receptor profile when this was not available (e.g. molindone).^{39,40} The next three columns show the relative side effect burden and efficacy according to a recent network meta-analysis³ whereby a lighter colour indicates a lower ranking for side effect burden or greater ranking for efficacy. Grey indicates data are not available. ‘Atypical’ drugs should have lighter colours across all three domains than ‘typical’ drugs. However, the figure illustrates that neither side effect burden or efficacy neatly map to this classification scheme.

C) Pharmacological differences between typical and atypical drugs The green bar on the left shows antipsychotics grouped into typical and atypical. The next three columns show the relative affinity for the dopamine D2 receptor, the serotonin 2A receptor and the ratio between the two. Affinities obtained from McCutcheon et al.³¹