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Analysis

How to classify antipsychotics: time to ditch dichotomies?

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Summary

The dichotomies of 'typical/atypical' or 'first/second generation' have been employed for several decades to classify antipsychotics, 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.

Keywords

Schizophrenia; pharmacology; nomenclature; psychosis; medication.

Over 20 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 past three decades the predominant classification of antipsychotic drugs has been into 'typical' and 'atypical' groupings. More recently the terms 'first' and 'second generation' have been used (Fig. 1(a)), but in practice this is used as a synonym for the typical/atypical 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 it is yet to be widely adopted (Fig. 1(a)). 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 sulpiride, which were observed to induce catalepsy in rats to a lesser degree than 'typical' antipsychotics such as haloperidol and chlorpromazine.[6] A formal definition, however, was not elaborated until the 1990s with a review by Kinon & Lieberman in which three criteria were specified: (a) a lack of extrapyramidal side-effects (EPSEs) and tardive dyskinesia; (b) increased therapeutic efficacy; and (c) minimal elevation of prolactin levels.[7]

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, whereas those developed subsequently came under the atypical umbrella. Figure 1(b) shows this classification against meta-analytical 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 and 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.[4] Moreover, there is no distinction in efficacy between the two categories. Even the archetypal antipsychotic, clozapine, although on average more effective than other antipsychotics, does not clearly separate in terms of efficacy from all typical drugs.[4,8]

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

Although 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 with atypical antipsychotics. However, even this difference is probably exaggerated owing to the nature of the trials that the meta-analytical estimates of side-effect burden are based on.

Antipsychotics antagonise dopamine D_2 receptors (D_2R) across the striatum,[9] including regions critical to normal movement, and it is therefore understandable that D_2R blockade can also lead to EPSEs. Positron emission tomography (PET) studies have shown that EPSEs are related to D_2R occupancy, and the risk is greatest when occupancy of dopamine receptors by dopamine antagonists exceeds ~85%.[10,11]

Receptor occupancy is related to dose and therefore, as expected, higher doses are associated with a greater risk of EPSEs.[12] PET studies indicated that the doses of typical antipsychotics used in many clinical trials, particularly the older ones, would be expected to result in D_2R occupancy >85%, whereas the doses of atypical antipsychotics used in clinical trials tend to be associated with D_2R occupancy <85%[13] This difference in D_2R 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 D_2R occupancy. For example, an important early trial of olanzapine used olanzapine doses in the range of 5–15 mg daily, compared with haloperidol doses of 15 mg daily in the comparator arm.[14] A dose of 15 mg olanzapine has been shown to be associated with around 70% occupancy of striatal D_2 receptors.[15] The dose of haloperidol required for similar occupancy is around 2.5 mg, with doses above 5 mg approaching 90% occupancy.[10,16] 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 D_2R occupancy to the atypical dose, rates of

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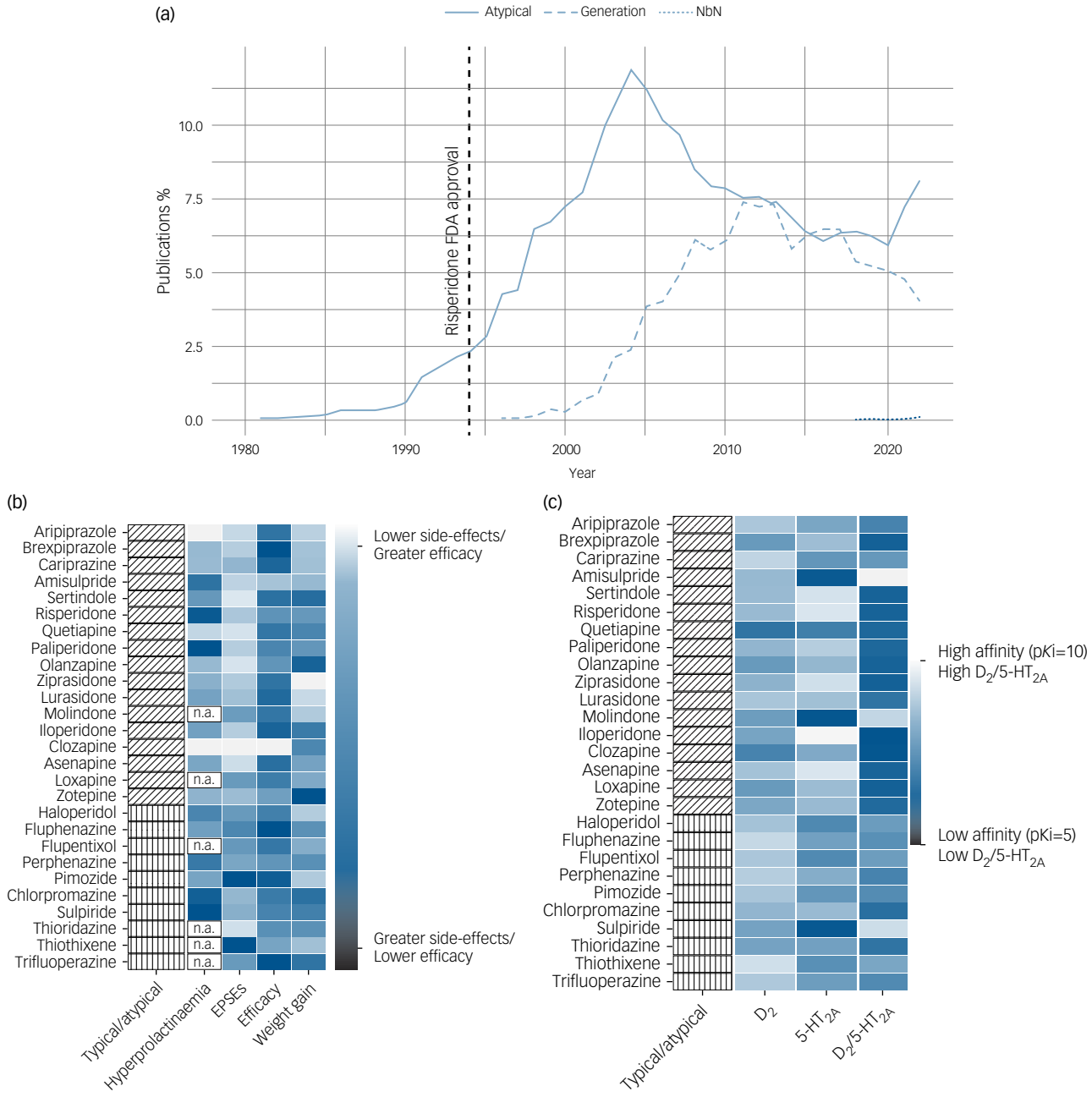

Fig. 1 Quantifying atypicality.

(a) Trends in nomenclature: to quantify the use of the 'atypical' terminology we searched PubMed using the search term 'atypical antipsychotic' to demonstrate what percentage of publications using the word 'antipsychotic' have employed this method of classification. We did the same for 'generation antipsychotic'. We then searched for citations of the first paper describing and recommending the pharmacology-based neuroscience-based nomenclature (NbN).[1] 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. FDA, US Food and Drug Administration. (b) Atypicality, efficacy and side-effects: the hatched bars show antipsychotics grouped into typical (vertical hatching) and atypical (diagonal hatching), as defined in clinical guidelines, or on the basis of receptor profile when this was not available (e.g. molindone).[2,3] The next three columns show the relative side-effect burden and efficacy according to a recent network meta-analysis,[4] whereby a lighter colour indicates a lower ranking for side-effect burden or higher ranking for efficacy. 'n.a.' indicates that data are not available; EPSEs, extrapyramidal side-effects. 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 maps to this classification scheme. (c) Pharmacological differences between typical and atypical drugs: the hatched bars show antipsychotics grouped into typical and atypical, as in part (b). The next three columns show the relative affinity for the dopamine D_2 receptor, the serotonin (5-HT) 2A receptor and the ratio between the two. Affinities obtained from McCutcheon et al.[5]

EPSEs between classes are similar.[17] Moreover, doses of atypical antipsychotics that would be expected to results in D_2R occupancy >85% are associated with higher rates of EPSEs.[18] 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 EPSEs also apply to prolactin effects.[19] 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.[20] There is no evidence, however, for a distinction in blood–brain barrier penetration along typical/atypical lines.[21]

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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 that the risk may be higher following long-term treatment with typical as opposed to atypical antipsychotics.[22] In this case the differences do not appear to be driven by dosing differences.[22] The limited number of studies that are available, however, make it difficult to determine whether 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 D_2R affinity rather than 'atypicality' may be the factor of interest.[23]

Although 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 (Fig. 1(c)).

Efficacy

Atypical antipsychotics were proposed not only to possess a more benign side-effect profile, but also to display greater efficacy. Initial trials supported this stance, but as evidence accumulated the proposed benefit appeared to be less clear.[4,24,25] A major blow to the hypothesis were the findings of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), funded by National Institute of Mental Health (NIMH).[26] In its first phase CATIE randomised over 1000 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 owing 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,[27] 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.[28] Later meta-analyses have confirmed that there is no clear distinction in efficacy along typical/atypical group lines.[4]

Similarly, early trials suggested that the atypical compounds were not only advantageous in terms of psychotic symptoms, but also that they showed a benefit in treating cognitive symptoms, a crucial domain given that no existing treatments appeared to show significant benefits here.[29] Again CATIE produced findings in contradiction of this hypothesis, with individuals on the typical treatment showing the greatest improvement in neurocognitive outcomes,[30] and network meta-analyses do not show any clear pattern of superiority for atypical over typical.[31]

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.[32] 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. Although antagonism of the dopamine D_2 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 (5-HT) 2A receptor relative to the affinity for the D_2 receptor was proposed as a key factor underlying atypicality.[33] Fig. 1(c) summarises the ratio of D_2 to 5-HT_{2A} affinities across the atypical/typical divide. This shows that, although the D_2 ratio separates a number of atypical and typical drugs, there are some notable exceptions. In particular, the D_2/5-HT_{2A} ratios of amisulpride, lurasidone and molindone overlap with those seen among typicals, whereas they would put thioridazine and chlorpromazine among the atypicals. Similarly, brexpiprazole fits with the atypical pattern of low D_2/5-HT_{2A} ratio, whereas cariprazine fits the typical pattern. Thus, the groupings do not reflect D_2/5-HT_{2A} ratios.

Although some separation exists between typical and atypical compounds based on D_2/5-HT_{2A} ratio, it is unclear as to why this mechanism should be afforded priority over others, given that its clinical relevance is unclear. That the ratio is unlikely to be central to efficacy is indicated by the fact that the most efficacious non-clozapine antipsychotic is amisulpride,[4] a drug that possesses negligible affinity for the 5-HT_{2A} receptor. It is also clear that other receptor systems play more important roles in determining side-effect burden, such as the histamine H_1 receptor for weight gain.[34] 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 typical/typical divide captures only a minimum of pharmacological differences at best.[5]

Other mechanisms proposed to underlie atypicality include 'fast dissociation' of drugs from the D_2 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 from (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.[35] From Fig. 1(c) we can see how an archetypal atypical compound, risperidone, shows greater affinity (and thereby slower dissociation) for the D_2 receptor than typical compounds such as sulpiride and thioridazine. Although k_{off} may well be an important mediator of clinical effects, it varies gradually across compounds (Fig. 1(c)) and it is therefore hard to see how it could be used to delineate a dichotomy.

In summary, the typical/atypical dichotomy was built on a presupposition that the antipsychotics that came to market in the years following the Food and Drug Administration (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 antipsychotic, is highly similar to one of the most recently approved antipsychotics, lurasidone, on all the Kinon & Lieberman criteria[7] and as regards D_2/5-HT_{2A} ratio (Fig. 1c). 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

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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 profiles.

Alternative classification schemes

Broad classification schemes such as the World Health Organization's Anatomical Therapeutic Chemical (ATC) system primarily classify medications on the basis of clinical indication, with more fine-grained categorisation based on chemical structure. Although broad categories are useful for facilitating epidemiological monitoring of drug use, the system is not suitable for clinical use, given that the chemically based subgroupings 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 the compounds share a common pharmacological mechanism (partial agonism of the dopamine D_2 receptor) and a similar clinical profile.[4] 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 D_2 partial agonism counters the D_2 antagonist's effects on D_2 receptors in the pituitary.[36] D_2 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 D_2 receptor occupancy levels (generally above 80%) seen at clinical doses with these drugs.[37] 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.[1] 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. 1(a)). 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 the make categories. For example although 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 H_1 receptor is central to the sedative and weight gain properties of a number of psychotropics.[34]

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,[5] 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 D_2 receptor (e.g. the partial agonists and lurasidone), one with serotonergic antagonism (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 ($TAAR_1$) agonists have recently shown efficacy in large clinical studies, and these appear distinct from existing antipsychotics because they do not block D_2 receptors and show different side-effect profiles.[38,39] Although 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, although 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 drugs are approved and suggest that 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 in 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 20 drugs and no schema to help guide the process. Fortunately, 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.[40]

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, they 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 the D_2/5-HT_{2A} 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 H_1 affinity is a better way to test this.

Conclusions

The classification of antipsychotics into two categories of typical and atypical has been the dominant taxonomic approach for over 30 years. Over this period, increasing evidence has accumulated that this category is fundamentally flawed in conception and

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application. As a result, the dichotomy now serves more to obscure than illuminate differences between compounds and we recommend that it is no longer used. Alternatives include NbN or a data-driven approach. 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 that 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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Data availability

Data availability is not applicable to this article as no new data were created or analysed in this work.

Author contributions

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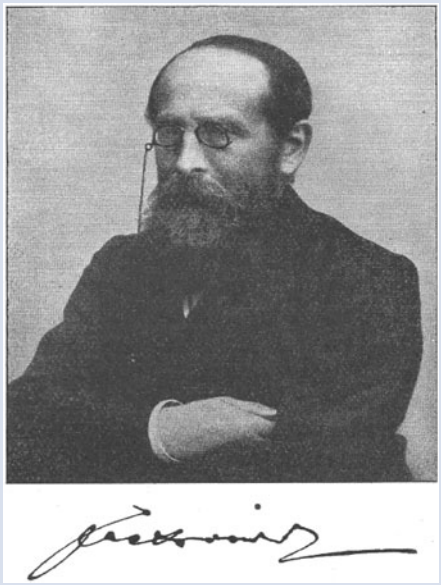
Psychiatry in history

Moritz Jastrowitz (1839–1912): moria madness, spider glial cells and X-rays

Madhusudan Dalvi



Very few psychiatrists recognise the term 'moria' (childlike euphoric excitement), coined by Jastrowitz in 1888, and even fewer will recognise 'Witzelsucht' (*witz* in German means wit and *sucht* is compulsion), coined by neurologist Hermann Oppenheim for a tendency to make silly puns. These terms have not found their way into Frederick Treves' German–English dictionary of medical terms. It was only after their description by Jastrowitz and Oppenheim that these become well-known as frontal lobe symptoms.

Moritz Jastrowitz trained in psychiatry, neurology and neuropathology and made exceptional contributions to glial cell anatomy. He was born in Lobau, Pomerania in Prussia to Hirsh Alexander and Ernestine and was eldest of six children in a struggling family. As a young boy he was forced to work in a shop but devoted his spare time to studying. He studied medicine at the Humboldt University of Berlin and the University of Zurich, qualifying in 1865. He became an assistant to Ludwig Traube at the Charité Clinic for internal diseases in Berlin and was later appointed chief physician in the psychiatry department under eminent psychiatrists Wilhelm Geisinger and Carl Westphal. In 1870–1871 he published a paper on the structure of nerve tissue during encephalitis in children in the early postnatal period, where he distinguished connective tissue from neuroglial cells and reported the presence of a molecular substance that he believed promoted myelination of axons during the development of the neuron but that gradually disappeared. He considered glial cells to be embryonic but believed they have a supportive role and described various shapes of glial cells (spindles, rounded, angular, cylindrical), reporting their length as being usually double or even three times their width. He described numerous processes extending from them, giving them a spider-like appearance, and hence named them 'spider glial cells' (*spinnenähnliche Gliazellen*) or 'spider cells' (*Spinnezellen*). He observed that their number increased towards the surface of the brain ventricle so that they finally formed the epithelium of the ependyma. This has paved the way for understanding the blood–brain barrier and neuroinflammation.

From 1881 Jastrowitz treated 12 cases of what he called moria. His first patient was a 38-year-old domestic servant who was admitted to Dalldorf for seizures, persecutory delusions, hallucinations and confusion. He would stand in front of other patients, open his eyes wide, joking and laughing. He misidentified attendants and physicians as former acquaintances and behaved in a childish manner, would whistle, suddenly cry out loudly or squeal in laughter and grab people. He died 6 years later and at autopsy was found to have a large right-sided frontal lobe tumour. In 1882 Jastrowitz was head physician at Maison de Santé in Schöneberg. In 1888 he wrote a textbook along with the distinguished neurologist Dr E. Leyden titled (in translation) *Contributions to the Theory of Localisation in the Brain and Their Practical Utilisation*. From 1891 Jastrowitz was in charge of a private psychiatric hospital Berolinum in Berlin-Steglitz. He published works on therapeutic effects of chloral hydrate, mental disturbance after head injury, aphasia, sufficiency of one hemisphere for motility, sensory activity and intelligence of the whole body. On 6 January 1896 Jastrowitz presented the discovery of X-rays at a session of the Berlin Association of Internal Medicine for the first time in Berlin. His son Hermann Jastrowitz was an eminent physician in Halle but was sadly a victim of the holocaust in Auschwitz. Jastrowitz died in Berlin aged 73, but moria under another name has survived and remains firmly embedded in the diagnostic criteria for frontotemporal dementia.

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