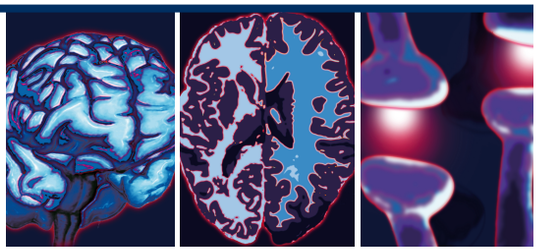
POLICY PERSPECTIVE



From 'classical' antipsychotics to 'multidimensional stabilizers': do we need a new classification for novel drugs used in schizophrenia?

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Practice points

- Novel compounds have a wider clinical efficacy compared with neuroleptics.
- The word 'antipsychotic' refers to a single pathological dimension in schizophrenia.
- New compounds have a prominent stabilizing action for both schizophrenia and bipolar disorder.
- The wider pharmacological action profile of novel compounds, compared with typical antipsychotics, accounts for their stabilizing activities.
- Other pharmacodynamic profiles are now under investigation in order to provide new compounds for the treatment of schizophrenia and bipolar disorder.

SUMMARY This article revisits the roots of the clinical categorical concept of schizophrenia and its biopathogenetic model ('dopaminergic model'), based on dopaminergic dysfunctioning in CNS, as conceived in the 1960s and 1970s. These clinical/biopathogenic concepts have been challenged by the dimensional approach and by a more complex neurochemical model of schizophrenia, arising mainly from the use of novel compounds, which involves activity on different neurotransmitters in the CNS. Moreover, new compounds used in the treatment of schizophrenia are effective not only on the psychotic dimension, but also on other dimensions, such as negative, depressive and cognitive ones. Therefore, the term 'antipsychotic', which refers to a class of drugs acting mainly on acute psychotic symptoms, seems obsolete, and schizophrenia should not be conceived as an acute disorder, but rather as a chronic multidimensional dysfunction. Consequently, novel compounds acting on different dimensions can better stabilize patients, avoiding the shift from positive to negative symptoms due to the D_2 antagonism. Thus, a new denomination is needed considering all of the peculiarities of new compounds compared with neuroleptics for stabilizing not just psychotic symptoms in the acute phase, but also affective, negative and anergic symptoms (which are integral parts of the disorder), even in the medium–long term; more appropriately, they should be considered as 'multidimensional stabilizers' instead of antipsychotics. Moreover, this denomination also refers to their efficacy in bipolar disorders, since their use is being increasingly proven to be effective in the treatment of this disorder as well. Finally, a change in the name of this pharmacological class may contribute to reducing the stigma that is now closely linked to antipsychotic drugs, such as chronicity, unfavorable prognosis and 'craziness'.

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The term 'antipsychotic', as it was conceived at the beginning of the 'psychopharmacological era', today seems to be obsolete and misleading for the clinical characterization of the new compounds used to treat schizophrenia. Actually, this term was linked to an outdated and over simplistic way of looking to a neurochemical model of schizophrenia, which was based on dopaminergic dysfunctioning, dating back to the 1960s/1970s. Moreover, it referred to a therapeutic strategy essentially built on the treatment of the acute phase of the disorder, and focused only on the positive symptoms.

In the 1960s, positive symptoms were considered the nuclear ones for schizophrenia, and the dopaminergic dysfunction linked to them appeared to be the main neurochemical systems responsible [1]. Therefore, it seems necessary today to redefine the way of using antipsychotics for the treatment of schizophrenia in light of the most up-to-date clinical, neurobiological and pharmacotherapeutic evidence that was obviously lacking at the time when Delay *et al.* coined the terms 'neurolepsis', and that of 'neuroleptic' for the first molecule that was effective on positive symptoms [2]. The aim of this article is to suggest a new definition of the compounds active on schizophrenia, starting from the clinical experience that arose from the use of new compounds, and from a clinical (dimensional) approach and based on psychobiological evidence collected in recent years.

In particular, the following aspects will be discussed:

- The evolution of the biological theories;
- The psychopathological dimensions (of schizophrenia);
- The 'atypicality' of new compounds, which is a confusing concept;
- Third-generation antipsychotics.

Evolution of the biological theories

From a clinical point of view, the current way of viewing schizophrenia greatly differs from 60 years ago when chlorpromazine was introduced. Accordingly, pharmacological treatments evolved dramatically during these years, often without a parallel advance in everyday clinical knowledge and in the theoretical approach to the therapeutic complexity of the disorder (i.e., different phases of treatment).

Kraepelin conceived of 'dementia praecox' as an early-onset severe psychotic illness, usually progressing to a dementia-like state. Some years later, Bleuler challenged the idea of unavoidable progress to dementia and refined the clinical picture of the disorder, emphasizing its heterogeneity in clinical phenomenology and outcome [3].

The beginning of the 'neuroleptic era' considered schizophrenia as being determined by dopaminergic dysfunctioning, thus viewing positive symptoms as the core or nuclear symptoms of the disorder. Dopaminergic dysfunction was confirmed in 1972 by Snyder *et al.*, who showed that psychotic symptoms could be worsened or elicited by amphetamine intake and that postsynaptic D_2 receptor blocking was related to the antipsychotic 'potency' of the different compounds [4].

More recently, the alteration of 'salience' (meaning the process of allocating meaning and relevance within the context of stimuli that the brain works with, in order to effectively manage the relationship with the external and internal world, selecting relevant stimuli from noise) seems to be related specifically to dopamine (DA) pathways. Antipsychotics may therefore lead to an improvement of symptoms by blocking postsynaptic D_2 receptors and so changing the 'salience' level [5]. In summary, dopaminergic dysregulation and impaired attribution of meaning and relevance (salience), combined with cognitive schemes that attempt to organize and make sense of these inputs, would lead to the emergence of psychotic symptoms [6]. Positive symptoms in schizophrenia are regarded as a state of dopaminergic hyperactivity in the cortical and subcortical structures (mesolimbic dopaminergic pathways), whereas negative and cognitive symptoms seem to be associated with dopaminergic hypofunction in associative cortical regions, such as the prefrontal and entorhinal cortex (mesocortical dopaminergic pathways) [7].

A different dopaminergic response has also been observed in mesocortical and mesolimbic systems secondary to the administration of neuroleptics, with these drugs having little effect on the dopaminergic tone of the prefrontal cortex (PFC) compared with that of striatal and limbic structures [8].

The PFC appears to be involved in working memory and related higher cognitive processes; therefore, the pharmacological activity on the dorsolateral PFC, primarily involving the DA D_1 receptor, may also modulate these cognitive functions [9–11].

The majority of MRI and PET studies, in accordance with the Kraepelin intuition about

the role of the frontal lobe in schizophrenia [12], showed a hypofunction of the PFC, which may be related to the cognitive symptoms that seem to be the landmark of the disorder together with negative symptoms, and certainly much more so than the positive symptoms [13]. Functional imaging studies (functional MRI and PET) also documented a hypofrontality in schizophrenia [14–19] as a peculiar aspect of the disorder, explaining cognitive impairments.

In recent years, new pathogenetic theories involving neurotransmitters other than DA have emerged; for instance, abnormalities in NMDA receptor (NMDAR) function could underlie negative and cognitive resistance to 'classical' antipsychotics. The DA hypothesis is not in contrast with the NMDA hypothesis; actually, DA and NMDARs share relevant interactions in various brain regions such as the hippocampus [20] or in the dopaminergic nuclei reached by glutamatergic pathways [21,22]. Enahancing NMDAR activity acting on glycine modulatory sites, as observed in placebo-controlled studies, may be an effective therapeutic choice for negative symptoms, and possibly for cognitive ones [23].

The persistent loss of the trophic effects of NMDAR activity may result in the cortical atrophy [24] and loss of dendritic spines [25–27], as observed in patients suffering from schizophrenia.

The efficacy of clozapine on the negative symptoms observed in schizophrenic patients [28,29] could be explained by its hypothesized reparative action, possibly mediated by NMDARs, although the efficacy of clozapine efficacy for treating primary negative symptoms is uncertain [30].

Furthermore, the neurotrophic and neuroplastic enhancements (provided by compounds acting via glycine modulatory sites) could be helpful for cognitive rehabilitation programs that do not appear to be consistently modified by the avalaible antipsychotic treatment [31].

Beside glutamatergic pathways, other neurotransmitters, such as serotonin (5-HT) or noradrenaline, seem to be implicated in a more complex neurochemical model of schizophrenia, as will be mentioned later [32].

Psychopathological dimensions

The theory about the origin and development of schizophrenia is based on a multifactorial model in which several genes interact with each other and with the environment or epigenetic factors, leading to different phenotypes in a 'continuum' between health and severe pathology [33].

DSV-IV is based on a qualitative taxonomy, in contrast to the forthcoming DSM-V, which will possibly be more dimensional and quantitative oriented. Therefore, the newer version should contain a quantitative specification that was not present in previous DSM versions: the cognitive dimension will probably be the first one to be added and evaluated.

The dimensional approach and 'continuum' theory for major psychoses are related to three main evidences [34]:

- Prevalence of 'subthreshold' psychotic symptoms or other 'spectrum' disorders in general population;
- Development of psychotic states in patients with a previous 'subthreshold' clinical picture;
- Identification of genetic and epigenetic risk factors.

Positive symptoms seem to have a 'continuum' distribution in the general population [35–37]; symptom prevalence in such 'nonclinical' samples varies from four to 17.5%, according to different ways of evaluating them [34,35]. Consequently, the psychotic phenotype seems to be much more widespread than supposed, especially for what concerns 'lifetime' prevalence [38].

Schizotypal personality disorder, characterized by susceptibility to subpsychotic experiences, also suggests the existence of a 'continuum' from normality, through eccentricity or different schizotypal conditions to schizophrenia. A factorial analysis of a schizotypal cohort has highlighted three different psychopathological dimensions: bizarre thoughts and perceptions; introversion and anhedonia; and conceptual disorganization [39]. This dimensional pattern is quite similar to schizophrenia.

Recently, it has been found that in a cohort of people with an 'at-risk mental state', a condition associated with a very high risk of psychosis, symptoms have a dimensional structure as in patients with schizophrenia, except for the positive dimension [40].

However, it should be clearly stated that psychotic dimensions are not specifically related to schizophrenia: psychotic symptoms can exacerbate neurological disorders (e.g., Alzheimer's disease, Huntington's disease, epileptic psychosis and vascular dementia) or be secondary to a drug intoxication or to dismetabolic conditions,

and they are similar to 'fever' for internal medicine, because they are ubiquitous in all the major psychoses and in the organic syndromes [41].

Presently, schizophrenia can be regarded as a neurodevelopmental and neurodegenerative disorder with a multifactorial etiology: this dimensional approach fits well in a polygenic inheritance hypothesis, which is probably the most reliable hypothesis in the explanation of the familial inheritability of the disorder. The assumption that several genes combine themselves following different patterns and subsequently interact with environmental factors is intuitively consistent with the idea that, accordingly to genotypes, individuals can be exposed to different (mild to severe) doses of risk factors [42]. A low environmental and genetic risk, according to this hypothesis, could lead to a condition similar to that of a schizotypal personality disorder or to focal deficits in particular areas (cognitive, neuropsychological or negative).

The use of a 'dimensional model' may also make genetic analysis easier, reducing the interindividual heterogeneity in schizophrenia: more homogenous phenotypes are potentially controlled by a smaller genetic set, and this can help the genetic investigation into the disorder [43]. In 1962, Meehl proposed the term 'schizotaxia' to describe a premorbid biological condition predisposing to the development of full-blown schizophrenia [44]: 40 years later, the concept is still valid, even in biopathogenetic terms, because the vulnerability to fall ill can be considered as the *primum movens* of the pathological process.

In general, dimensional models may be able to predict more precisely the course, outcome and treatment response [45,46] in a single patient.

But which are the main psychopathological dimensions to be considered? Originally, in the beginning of 1980s, a binary model was considered with positive and negative dimensions underlying possible different biopathogenetic determinants [47–49].

Actually, the first factorial analysis highlighted a symptomatological pattern consisting of three main psychopathological dimensions: positive, negative and disorganized [50–52]. However, this tridimensional model has also been criticized for its excessive simplification of the clinical picture [53].

Successively, a five-dimension model (based on factorial analysis) consisting of negative, delusional, hallucinatory, disorganized and depressive dimensions has been proposed [54]. Moreover, even an eight-dimension model has been suggested (consisting of psychotic, disorganized, negative, manic, depressive, excitatory, catatonic and 'absence of insight' dimensions) [54].

The pentadimensional model (negative, positive, depressive, disorganized and impulsive dimensions) seems the best model to represent the whole range of multifaceted syndromal patterns of schizophrenia [55,56]. Unfortunately, this model excludes the cognitive dimension, considering it to be secondary or influenced by other psychopathological dimensions and not as a primary and autonomous one. This view contradicts clinical evidence that clearly shows, as Kraepelin pointed out, that cognitive deficit is an early marker of the disorder [57], not secondary to the dysfunction of other psychopathological domains.

Today, cognitive deficits can no more be considered as an epiphenomenon of schizophrenic disorder; rather, they should be seen as one of its peculiar traits [58,59], and this point will be taken into account in DSM-V. Actually, cognitive impairments usually precede the onset of clinical symptoms [60–64]; in this light, they cannot be seen as a consequence of antipsychotic treatment [65]. Moreover, other findings confirm their stability over the course of illness [66,67], not merely related to its duration [68]. These data seem to suggest that cognitive deficits should be considered as an endophenotype of the disorder. This latter term, introduced by Gottesman and Shields [69], is defined as "measurable components unseen by the unaided eye along the pathway between disease and distal genotype" [70]. Endophenotypes are characterized by five critical features [71]: they are associated with the disorder but they take no part of its diagnosis; they are heritable; they are state independent; they cosegregate with illness in families; they can be highlighted in unaffected siblings at a higher rate than in the general population.

Following this point of view, a correlation has been sought between the cognitive dimension and other psychopathological dimensions, in order to understand which symptomatological pattern was more related to cognitive deficits.

In general, cognitive impairments, clearly evident in various superior functions (executive function, abstract thinking, concentration and verbal fluency), seem to have little correlation

with the severity of dysfunction in the other symptom dimensions. This could suggest a widespread cortical impairment, affecting more than a single neural circuit, which seems stable over time and almost independent from the course of the disorder [72].

In this context, it is worth mentioning the concept of 'cognitive dysmetria' [73], a kind of integrative theory of discognitive impairments present in schizophrenia. It takes into account three key brain regions: prefrontal regions, thalamic nuclei and the cerebellum. Alterations in these areas, or at the level of the interconnections, among these would be able to produce the 'cognitive dysmetria', or difficulties in selecting, processing, coordinating and responding to internal and external stimuli. This 'poor mental coordination' is to be regarded as the fundamental deficit in schizophrenia, and is probably responsible for a wide range of symptoms.

The presence of cognitive disorders in childhood was first highlighted in patients who later developed schizophrenia [74–76]. Data from large samples of military recruits have reported the presence of impaired intellectual functioning well before the onset of the disorder [77,78].

From this perspective, cognitive dysfunctions seem to be a risk factor for the future onset of the rest of the clinical picture; this disability represents a real limitation of a patient's functional outcome and quality of life [79–81].

Cognitive dysfunctions (verbal learning and memory, vigilance and executive functions, among others) are as important (or even more so) as positive or negative symptoms for the prediction of a patient's functional outcome [82–85].

Positive or impulsive dimensions, including suicidal behavior [86] and their response to antipsychotic treatments, do not seem to be related to the cognitive dimension [87]. The disorganized dimension has little evidence of a correlation with the cognitive dimension, but it usually does not respond to 'classical' antipsychotic treatment [88]. Some other studies found a relationship between negative–depressive dimensions and cognitive dysfunction [87,89]. Atypical antipsychotics seem to be able to act on cognitive functions [90]; in addition, they do not cause major extrapyramidal symptoms [91–93].

Atypicality of new compounds: a confusing concept

The history of the pharmacological treatment of schizophrenia reflects that of the disorder itself. Since their introduction, antipsychotic drugs were utilized for the treatment of acute schizophrenic symptoms and, even now, these drugs are seen as beneficial for the acute phases, with a minor emphasis on relapse prevention.

From a theoretical point of view, drug treatment with 'classical antipsychotics' reflects the idea that this was primarily related to DA pathway dysfunction, which is often responsible for the acute clinical picture (delusions and hallucinations).

As previously mentioned, we now know that serotonergic pathways (and their interactions with DA) are probably implicated in the wider spectrum of the efficacy of atypical antipsychotics. The serotonergic:dopaminergic ratio and interactions represent the relevant factors that can at least partly explain the efficacy and tolerability of second-generation antipsychotics (SGAs) [94–96] compared with neuroleptics.

Most atypical antipsychotics share a reduction in D_2 antagonism and a higher occupancy of 5-HT_2 receptors compared with older compounds. Affinity ratio between 5-HT_{2A} and D_2 receptors has been considered as an 'atypicality index' [97].

5-HT_{2A} receptors appear to already be blocked even at low dosages of an atypical antipsychotic, while their antipsychotic activity seems to start over the 65% threshold of D2 receptor occupancy. The extrapyramidal syndrome (EPS) threshold for neuroleptics and for atypicals is higher, at 80% of D_2 receptor occupancy. The transient occupation of D_2 receptors and their rapid dissociation can explain the better tolerability of some atypicals, notably clozapine and quetiapine. This mechanism avoids increases in plasma prolactin, does not affect cognition and could reduce the occurrence of EPS [98]. Detaching from D_2 receptors within 12–24 h (fast-off D_2 theory) [99] could account for the modest extrapyramidal activity of clozapine and quetiapine, resulting in less Parkinsonian symptoms or tardive dyskinesia [100]. By contrast, classic antipsychotics do not fast release from D_2 receptors, remaining coupled for longer periods, leading to accumulation and consequently, in some cases, causing tardive dyskinesia [100].

Some atypicals, notably clozapine and quetiapine, clinically help patients by transiently occupying D_2 receptors and then rapidly dissociating to allow normal DA neurotransmission. This mechanism keeps prolactin levels normal, spares cognition and does not elicit burdensome EPS [98]. While 5-HT_{2A} receptors are readily

blocked at low dosages of most atypical antipsychotic drugs, the dosages at which this happens are below those needed to alleviate psychotic symptoms. The antipsychotic threshold occupancy of D_2 for antipsychotic action remains at approximately 65% for both typical and atypical antipsychotic drugs, regardless of whether 5-HT_{2A} receptors are blocked or not. At the same time, the antipsychotic threshold occupancy of D_2 receptors for eliciting EPS remains at approximately 80% for both typical and atypical antipsychotics, regardless of the occupancy of 5-HT_{2A} receptors.

The 'fast-off D_2' theory, on the other hand, predicts which antipsychotic compounds will or will not produce EPS and hyperprolactinemia, and which compounds present a relatively low risk for tardive dyskinesia. This theory also explains why L-DOPA psychosis responds to low atypical antipsychotic dosages, and it suggests various individualized treatment strategies [99]. Clozapine and quetiapine do not elicit Parkinsonism and rarely result in tardive dyskinesia because they detach from D_2 receptors within 12–24 h. Traditional antipsychotics remain attached to D_2 receptors for days, preventing relapse, but allowing accumulation that can lead to tardive dyskinesia [100]. From a clinical point of view, these compounds seem to be characterized by the following features: they cause low extrapyramidal side effects at clinically effective doses, they have less propensity to elevate serum prolactin levels; and they possibly have greater efficacy for reducing negative symptoms. Atypicals may also have a better effect on cognitive function (at least not deteriorating it) and on improving the ability to cope with mood symptoms than neuroleptics [101,102].

But there are no stringent and accepted criteria to define 'atypicality'. In fact, some SGAs, such as risperidone, olanzapine or amisulpride, have to be considered as 'partially atypical' because they may cause 'typical' side effects (EPS and prolactin elevation) when used at a higher dosage, particularly risperidone and amisulpride.

The more intriguing and peculiar activity of SGAs consists of their ability to better stabilize patients, leading to a better prevention of relapses, a lack of inducing secondary depressive or anergic symptoms, ameliorating negative symptoms without stimulating or worsening psychotic behavior [103] and preventing deteriorating cognition, which allows for a better implementation of rehabilitative programs [104].

Presently, apart from clozapine (originally used for drug resistance [105]), there are other atypical compounds, such as quetiapine, risperidone, olanzapine, amisulpride, aripiprazole, ziprasidone and paliperidone.

From a pharmacodynamic point of view, clozapine has high affinity for D_4, 5-HT_2, α_1, muscarinic and histaminic receptors, and a relatively weak affinity for D_1, D_2 and D_3 receptors, whereas olanzapine is more effective on D_2 receptors and has a weaker affinity for D_4 and α_1 adrenergic receptors compared with clozapine. Quetiapine shows weak affinity for 5-HT_{1A}, 5-HT_2, D_1, D_2, H_1 and α_{1-2} receptors and an elevated 5-HT_2:D_2 ratio. Finally, risperidone and paliperidone have a D_2 antagonism associated with a powerful antagonist effect on 5-HT_2 receptors, allowing for efficacy on negative and positive symptoms.

As mentioned before, the term 'atypical' is misleading for defining this novel class of drugs; in fact, their side-effect profiles and their mechanisms of action are dramatically dissimilar between each drug, and therefore it is intuitive to try to find a new and more meaningful denomination.

First-generation antipsychotics should still be used, for a limited period of time, in some particular clinical situations, such as treatment of agitated patients, in an emergency room or in general for violent behavior related to acute psychotic states [106,107]. Large population studies, such as the CATIE study, did not confirm the SGA superiority and found that perphenazine was just as effective as SGA in the treatment of schizophrenia. Despite being derived from large randomized controlled trials, these results are controversial because of some methodological limitations such as the short- to mid-term outcomes that were measured, the absence of functional and wellbeing scores and the gap between the 'real population' (characterized by multidimensional deficits and the prevalence of negative–anergic symptoms and substance abuse) and the examined population (prevalence of chronic patients and of acute positive symptoms) [108,109]. Hence, the use of first-generation antipsychotics in a long-term treatment strategy could be considered as malpractice, because of their low tolerability ratio, low patient compliance, limited activity on dimensions other than the positive ones, risk for deteriorating cognition and poor clinical stabilization [103].

Third-generation antipsychotics

For the near future, beside the synthesis of new compounds, we should aim to obtain drugs that achieve:

- More efficacy at reducing relapses and negative and cognitive dysfunction in schizophrenia;
- Reduced incidence of metabolic syndromes or heart toxicity than dopaminergic/serotonergic compounds (i.e., SGAs).

Pharmacological engineering is now working on several new compounds that are active on different receptors. Nicotinic, muscarinic, glycinergic, glutamatergic, cannabinoid and GABAergic receptors are now under investigation.

Xanomeline, a relatively selective muscarinic type 1 and type 4 receptor agonist, has been tested in a preclinical trial compared with placebo; xanomeline showed significant effectiveness on the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) scores, and in the cognitive test battery (particularly verbal learning and short-term memory) compared with placebo [110].

A neurokinin (NK) 3 antagonist, a 5-HT antagonist, a central cannabinoid antagonist and a neurotensin antagonist have been studied with identical protocols in order to assess their safety and efficacy [111]. The group receiving 5-HT_{2A} antagonists showed a reduction in PANSS total and negative symptom scores, compared with the placebo group. The efficacy showed by NK3 and 5-HT antagonists was smaller than that observed in the haloperidol group, even if the NK3 effectivity was positively correlated with plasma levels. On the other hand, the cannabinoid receptor 1 and neurotensin receptor antagonists did not show any difference compared with the placebo group, even if the study limitations do not allow for asserting definite statements on these compounds.

A recent Phase II clinical trial demonstrated the antipsychotic efficacy of a compound with agonist activity for mGluR2/3, which have been implicated in the pathophysiology of schizophrenia. In this regard, the mGlu3 protein has been found to be decreased in dorsolateral PFC in schizophrenic patients (no difference has been observed for mGlu2). These proteins have been found to be related with enzyme (GCP II) and ligand (NAAG) anomalies in schizophrenia, suggesting an impairment of these circuits is involved in the pathogenesis of the disorder [112–115].

On the other hand, it is worth mentioning a large randomized trial testing glutamatergic agent efficacy on negative and cognitive symptoms that did not find any differences with the placebo group [116].

There is now substantial evidence that GABA signaling is deficient in corticolimbic regions, particularly in the dorsolateral PFC and hippocampus of patients with schizophrenia. In this regard, it is worth mentioning BL-1020, a compound consisting of the antipsychotic drug perphenazine and GABA. This compound, studied in a preclinical setting, was efficacious in rodents, where it has been observed to have significantly reduced side effects compared with the administration of perphenazine alone. Subsequently, Phase II clinical trials on schizophrenic patients showed clinical improvements, even though further data are needed to define the overall clinical efficacy of BL-1020 [117].

α_7 nicotinic receptor agonists showed efficacy, especially on the cognitive dimension, while their action on the positive dimension seems to be minimal [118]; this kind of compound demonstrated a facilitating activity on cognitive function, notably on learning and memory tasks, in human and in rodents [119]. It has also been proven that these compounds are effective on attentional and sensory deficits in schizophrenic patients [120,121].

A different approach for the upcoming drugs for schizophrenia involves the inhibition of GlyT1-mediated transport [122]: GlyT1 is the type 1 glycine transporter that regulates glycine levels adjacent to the NMDARs that are glutamate receptors, which have recently been shown to be involved in schizophrenia's molecular basis. Actually, an important role for the most relevant psychopathological fields in schizophrenia may be played by glutamatergic neurotransmission [123].

Historically, the glutamatergic hypothesis of schizophrenia was originally based upon clinical observations of chronic abusers of phencyclidine (an NMDAR antagonist). Phencyclidine use can cause thought disorder, emotional blunting, working memory disturbances and auditory hallucinations [124]. More recently, ketamine, an NMDAR antagonist, has proven to be able to provoke analogous effects in healthy volunteers [125]. These data support the hypothesis that a hypofunction in NMDARs may be a relevant mechanism for understanding the pathophysiology of schizophrenia.

Accordingly with this hypothesis, drugs combining anti-DA activity and NMDA enhancement have been designed to act on cognitive, emotional and psychotic symptoms in schizophrenia [126,127]. However, a recent multicentric study did not show positive results for this therapeutic intervention [128].

Conclusion

In recent years, theoretical and practical approaches to psychoses, and namely to schizophrenia, have widely changed. On the one hand, increasing evidence seems to demonstrate the differential expression of the psychotic phenotype well below its clinical manifestation (e.g., schizotipy, psychotic experience and psychosis proneness, among others), questioning the correlation between symptoms and syndromes. Thus, the artificial division into the two groups according to symptomatology and course of the disorder (schizophrenia vs mood disorders) is presently challenged [41,129].

On the other hand, as an overall therapeutic strategy, long-term treatment seems essential for coping with relapses and, differently from that of the 1960s and 1970s, strategies are no longer focused on the use of these compounds in the acute phase or episode, but in the long term instead. In the 1960 and 1970s, schizophrenia was in fact conceived to be the summation of several acute episodes, regardless of the intercritical periods, which are essential for preventing relapses and where reaching a clinical stabilization is crucial for long-term outcomes.

Today, stabilization and relapse prevention (maintenance) have to be considered as primary therapeutic goals in schizophrenia and major psychoses, acting mainly on the different psychopathological dimensions. In this respect, the novel drugs, compared with neuroleptics, represent a major step forward for long-term management, and they have potential for reducing relapses and possibly brain neurodegeneration [130].

The old compounds were closely related to the equation 'DA = positive symptoms = schizophrenia': this is based on a cause–effect relationship that ignored the complexity of the neurochemical dysfunctioning of the disorder, involving other neurotransmitters such as 5-HT and glutamate and not just DA.

These new compounds are defined as 'atypicals', which is a vague definition and cannot be acceptable for future use regarding these drugs: it seems better to use the term 'stabilizer' in the sense that they reduce the 'shift' from positive to negative–anergic polarities, as caused by the use of neuroleptic drugs [105,131], and making the patient more amenable for integrated nonpharmacological treatments (e.g., rehabilitative or family therapy). Moreover, the term 'antipsychotic', referring only to the psychotic dimension, is confusing nowadays and charged with a heavy stigma. The term 'antipsychotic' emphasizes only the activity of the psychotic dimension; actually, we need to stress that new compounds act on multiple dimensions, such as negative, disorganized, impulsive–aggressive, depressive and cognitive ones.

Thus, a better classification for the available and future compounds that are active on schizophrenia could be that of 'multidimensional stabilizers', due to their ability to be effective in both the acute phase and maintenance phase of the disorder and on different psychopathological dimensions.

In other words, replacing the term 'antipsychotic' with that of 'multidimensional stabilizer' drugs also highlights the capability for a better stabilization in the long term, and probably the potential ability to counteract the neurodegenerative processes in the CNS, as evidenced by some recent neuromorphological studies [132].

In conclusion, if on the one hand the approach to the treatment of schizophrenia can no longer be that from the 1960s and 1970s [133], instead needing to be holistic with rehabilitative and psychoeducational purposes (on the basis of the gene–environment interaction model), on the other hand, the ability of novel medications acting in a multidimensional way on the different neurochemical dysfunctions of schizophrenia (involving not only DA but other neurotransmitters and neuromodulators in the CNS) needs to be stressed, and it is necessary to change an old classification of the compounds that are effective on a variety of schizophrenic symptoms.

Future perspective

The advent of atypical antipsychotics in recent years has partly changed the management of schizophrenia, even if the prognosis of the disorder still remains unfavorable because of the limited efficacy of new compounds on some symptomatological dimensions (e.g., negative and cognitive dimensions) and because of the burden of some side effects, primarily metabolic syndrome. In the coming years, psychopharmacological research should provide new drugs with

different mechanisms of action or different pharmacodynamic properties for both schizophrenia and affective disorders. Molecules acting on neurotransmitters other than dopamine and serotonin, such as glutamatergic, glycinergic and GABAergic receptors, are now under investigation for future use in the clinical settings. Moreover, different pharmacodynamic profiles should be investigated to improve clinical stability and patient compliance. This will possibly lead to an improvement of functional and clinical outcomes of schizophrenia, and will hopefully help in the discovery of the underlying etiopathogenic mechanisms of the disorder [109].

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