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Nervous system disorders

Developing selectively nonselective drugs for treating CNS disorders

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For the past two decades, drug discovery has been dominated by the ‘magic bullet’ or single molecular target-based approach. But for many diseases of the central nervous system, especially complex polygenic disorders such as schizophrenia, the most effective drugs have affinity for many molecular targets. Various methods have been recently proposed for developing so-called ‘selectively nonselective drugs’ or ‘magic shotguns’ – that is, therapeutics with more complex pharmacological profiles.

Introduction

Since the early 1980s, when the ability to screen compounds at receptor targets increased, a ‘one-disease one-target’ paradigm has dominated the pharmaceutical industry. Even though a target-based approach is ideal from a scientific and practical perspective, it has generally not translated into a high success rate for developing truly novel CNS medications. The pharmaceutical industry has continued to focus on finding additional compounds that hit known and validated targets (‘me too’ drugs). This cannot continue indefinitely, however, and thus it is critical to find new approaches to CNS drug development. Recently, several authors have proposed that designing selectively nonselective drugs that interact with several molecular targets (coined ‘magic shotguns’ [1]) will lead to more effective medications for a variety of complex disorders [1–3]. In this review, we will discuss the

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advantages and disadvantages of various proposed methods for developing these so-called magic shotguns.

Are ‘dirtier’ drugs better for psychiatry?

The idea that promiscuous drugs might be more effective than selectively targeted drugs in CNS disorders has emerged from the study of clozapine, the first ATYPICAL ANTIPSYCHOTIC drug (see glossary, Box 1). Clozapine displays an extremely complex pharmacological profile that is thought to underlie both clozapine’s superior clinical efficacy and its spectrum of potentially life-threatening side effects [1]. As such, much of the goal in antipsychotic drug development has been to create clozapine-like drugs that bind to fewer targets and thus reduce side effects. Similarly, antidepressants affecting multiple targets have better efficacy than single target agents such as the SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs, see glossary), although often at the expense of increased side effect burden. Indeed, MONOAMINE OXIDASE INHIBITORS (see glossary) and TRICYCLIC ANTIDEPRESSANTS (see glossary) are likely to be superior to SSRIs, especially for treatment-resistant depression [4], although they are limited in use because of side effects. Development of newer antidepressants has used this knowledge to design so-called ‘dual-action’ antidepressants that inhibit the reuptake of both serotonin and either dopamine or norepinephrine. These dual-action antidepressants

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Glossary

Agranulocytosis: an acute condition involving a severe and potentially fatal reduction in white blood cells that is a rare, idiosyncratic reaction to several different drugs, including the atypical antipsychotic clozapine.

Atypical antipsychotics: a second generation of antipsychotic medications characterized by less extrapyramidal side effects than older antipsychotics. The exact definition of atypicality remains debated.

Extrapyramidal side effects: the various movement disorders that result from taking dopamine antagonists, particularly antipsychotic drugs, that include dystonias (severe muscular spasms often of the neck, eyes, tongue, or jaw), drug-induced parkinsonism (muscle stiffness, shuffling gait and tremor), and tardive dyskinesia (involuntary, irregular muscle movements, usually in the face).

Monoamine oxidase inhibitors: a class of antidepressant drugs that reversibly or irreversibly inhibit the enzyme monoamine oxidase which metabolizes monoamines such as norepinephrine, dopamine and serotonin.

Pharmacophore: defined loosely to refer to the functional or structural elements of a compound that possess biological activity.

Selective serotonin reuptake inhibitors: a class of antidepressant drugs that act by blocking the reuptake of serotonin from the synaptic cleft.

Tricyclic antidepressants: a class of antidepressant drugs that contain three fused benzene rings and that block the reuptake of the norepinephrine, serotonin, and to a lesser extent dopamine from the synaptic cleft.

have been shown to be more effective than 'single-action' antidepressants such as the SSRIs [5,6], although they are probably still inferior in efficacy to the tricyclic antidepressants and monoamine oxidase inhibitors. Clearly, multi-action agents are likely to be more effective than single-action agents in many CNS disorders; thus, the challenge is to identify novel ways to design and to discover such magic shotguns. Below we review some conventional and non-conventional strategies currently being explored for developing selectively nonselective medications (Table 1).

Multidrug therapy

For decades, clinicians in many fields including psychiatry have combined medications in an often-desperate (and usually off-label) attempt to achieve a clinical effect in their most treatment-resistant patients [7]. For many non-psychiatric diseases, multidrug therapy has become the standard of care with the treatment of hypertension, diabetes and HIV infection being prominent examples [8–10]. Indeed, multiple drugs are often packaged into a single pill for ease of administration (e.g. hydrochlorothiazide-beta-blocker combinations in the treatment of hypertension). Successful development of a multidrug combination requires each drug to be independently efficacious and safe or that a second compound have a defined mechanism of action that clearly enhances the action or inhibits the metabolism of the first drug (Fig. 1a). Examples of the latter include the concomitant administration of L-DOPA (L-4-dihydroxyphenylalanine) with catechol-O-methyltransferase inhibitors in the treatment of Parkinson's disease and in the treatment of infections with amoxicillin

Box 1.

Clozapine, the first of the atypical antipsychotic drugs, was developed in 1958 as a chlorpromazine analog but was initially rejected as an antipsychotic drug because it did not cause extrapyramidal side effects in rodents, the predominant animal model predicting antipsychotic efficacy. However, after years of clinical use in Europe and subsequent approval in the United States in 1989, it has become the 'gold standard' antipsychotic medication because of this absence of debilitating extrapyramidal side effects and its demonstrated clinical superiority in treating schizophrenia [37]. Clozapine is, however, associated with its own set of serious side effects including weight gain, diabetes, an increased risk of seizures and AGRANULOCYTOSIS (see glossary). Clozapine displays an extremely complex *in vitro* pharmacological profile, with nanomolar affinity for many neurotransmitter receptors, including dopamine (D₄), serotonin (5-HT_{2A}, 5-HT_{2C}, 5-HT₆, 5-HT₇), muscarinic (M₁, M₂, M₃, M₄, M₅), and adrenergic (α_1 , α_2) receptors [1]. This rich pharmacology is thought to underlie both clozapine's superior clinical efficacy and its spectrum of potentially life-threatening side effects. As such, much of the goal in antipsychotic drug development has been to create clozapine-like drugs that bind to fewer targets and thus reduce the side effect burden by targeting only the appropriate receptors. Attempts to target clozapine's 'magic receptor' have been largely been unsuccessful. For example, D₄-selective antagonists [38], as well as combined 5-HT_{2A}/D₄ antagonist [39], are ineffective in treating schizophrenia. The 5-HT_{2A} selective compound M100907 [40], although more effective than placebo, failed to reduce symptoms to the same extent as haloperidol (a typical antipsychotic drug comparator). The 5-HT_{2A/2C} antagonist SR46349B fared only marginally better versus haloperidol [41]. Thus, it has become apparent that compounds with rich pharmacology may be more effective in the treatment of schizophrenia [1].

along with the beta-lactamase inhibitor clavulanic acid. Could such an approach work for psychiatric disorders?

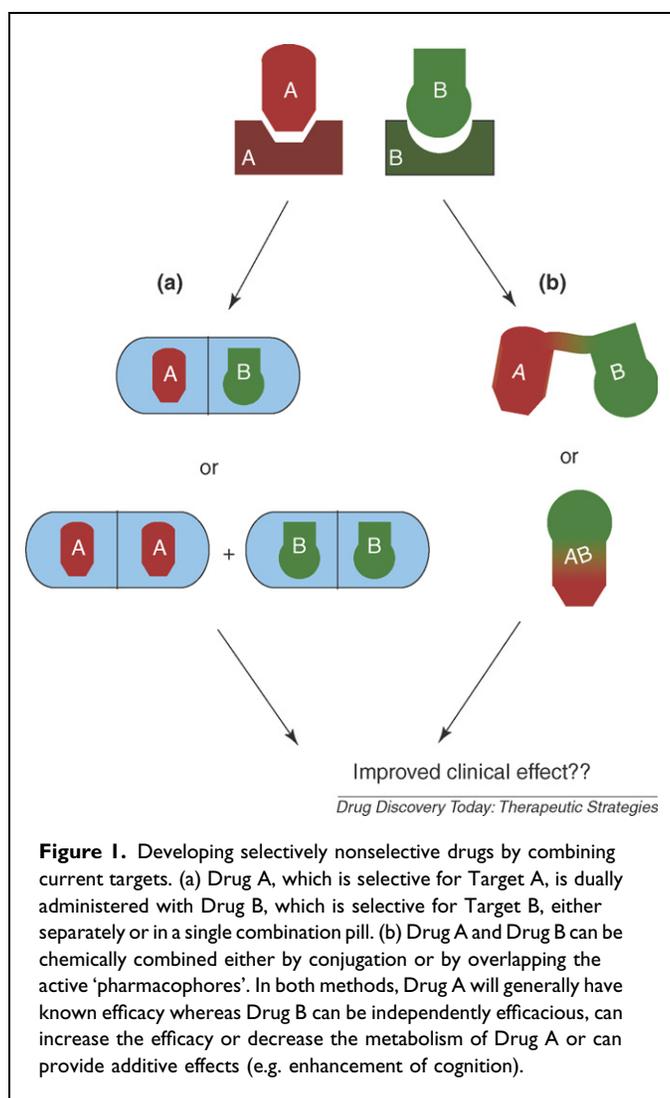
Because the etiology of psychiatric disorders such as schizophrenia and depression is unknown, it is difficult to rationally make useful drug combinations for treating these illnesses. However, a few strategies involving multidrug therapy have been recently suggested. For example, a major hurdle in the treatment of depression is the slow onset of action of all existing antidepressants. This lag likely represents ill-defined neurobiological adaptations that ultimately result in clinical improvement [11,12]. Augmentation of current antidepressants with 5-HT_{2A} receptor antagonists (e.g. M100907) or with compounds selective for non-monoaminergic targets (e.g. neurokinin-1 receptor antagonists) might be useful to hasten the action of current antidepressants [13].

It has also recently been suggested that independently treating the different elements of schizophrenia, such as positive and negative symptoms, cognitive impairment and suicidality, might be a useful way to approach this devastating illness [14]. Indeed, the cognitive impairment associated with schizophrenia is generally thought to be the most disabling component of the disease and thus current antipsychotics could be augmented with cognition-enhancing agents. For instance, because the M₁-muscarinic agonist properties of the clozapine metabolite *N*-desmethyl-clozapine [15,16] are predictive of the pro-cognitive actions of

Table 1. Strategies for developing selectively-nonselective drugs for CNS^a disorders

Strategy	Pros	Cons	Examples of recent developments	Who is working on this strategy?	Refs
Multidrug therapy	Can treat multiple domains of dysfunction separately Allows continuation of current single-target approach with multiple single-targets Can enhance the actions of currently available drugs	Unable to fully recreate superior efficacy of highly promiscuous drugs Problems with pharmacokinetics Increased side effect burden and potential for toxicity Problems with patient compliance	Fluoxetine/olanzapine combination drug in the treatment of bipolar depression (Symbyax [®] , Eli Lilly and Co., http://www.lilly.com/)	Various private and public sector laboratories attempting to identify highly-selective ligands for multiple CNS targets	[34]
Designed multiple ligands	Takes advantage of proven medicinal chemistry techniques with development of entirely new paradigms Can rationally combine proven molecular targets New leads can be tested in already validated model systems	Unable to fully recreate superior efficacy of highly promiscuous drugs Unclear which targets would be best to combine Often creates large molecules with poor pharmacokinetic profiles If affinities are not balanced, need larger doses and thus increased risk of toxicity	Duloxetine, a dual-action (serotonin and norepinephrine reuptake inhibitor) with indications for major depression and diabetic neuropathy (Cymbalta [®] , Eli Lilly and Co., http://www.lilly.com/)	Various private and public sector medicinal chemistry laboratories	[35]
High-throughput behavioral screening	Allows screening at the level of the entire organism Does not rely heavily on known mechanisms and targets of drug action Leads likely have favorable pharmacokinetics Potential for novel drugs with superior efficacy	Relies heavily on current animal models that have variable predictive value Logistically difficult, requires large numbers of animals	Two novel antidepressants currently showing promise in early-phase trials: YKPI0A (Janssen Pharmaceuticals, http://www.janssen.com/) and nemifitide (Tetragenex Pharmaceuticals, http://www.innapharma.com/)	PsychoGenics (Tarrytown, NY) (for one) http://www.psychogenics.com/	[28,29]
Genomics-based screening	Allows screening at whole animal, systems and cellular levels Does not rely heavily on known mechanisms and targets of drug action Potential to target underlying cause of disease by normalizing gene expression patterns Potential to yield new insights into pleiotypic drug actions Potential for novel drugs with superior efficacy	Human disease signatures from post-mortem samples likely confounded by life-long drug treatments and effects of aging Cell systems <i>in vitro</i> do not fully represent <i>in vivo</i> physiology likely with significant differences in gene expression	A novel compound, PGX5188 (Psychiatric Genomics, http://www.psygenomics.com/) was identified as having a similar gene modulation signature as valproate in human neuroblastoma flat cells and thus may have therapeutic potential	Psychiatric Genomics, Inc. (Gaithersburg, MD) (for one) http://www.psygenomics.com/	[14,36]

^a Central nervous system.



clozapine; it has been suggested that M_1 -agonists might be useful as 'add-on medications' for enhancing cognition. Additionally, 5-HT₆ receptor antagonism increases acetylcholine- and glutamate-mediated neurotransmission thereby enhancing cognitive processes [17], suggesting a use for these compounds in cognitive-enhancement in schizophrenia [18].

There are, however, distinct disadvantages to the use of multidrug therapies including problems related to differential pharmacokinetics, the risk of additional side effects and toxicities, and concerns with patient compliance. In addition, the development of multi-component pills for use in psychiatric disorders could be difficult because often one or both compounds need to be titrated independently to maximize clinical effect. At best, multidrug therapy, especially in psychiatric disorders, could act as a bridge to the development of single multi-target compounds.

Designed multiple ligands

In recent years there has been an increasing trend in medicinal chemistry for the deliberate and rational design of drugs

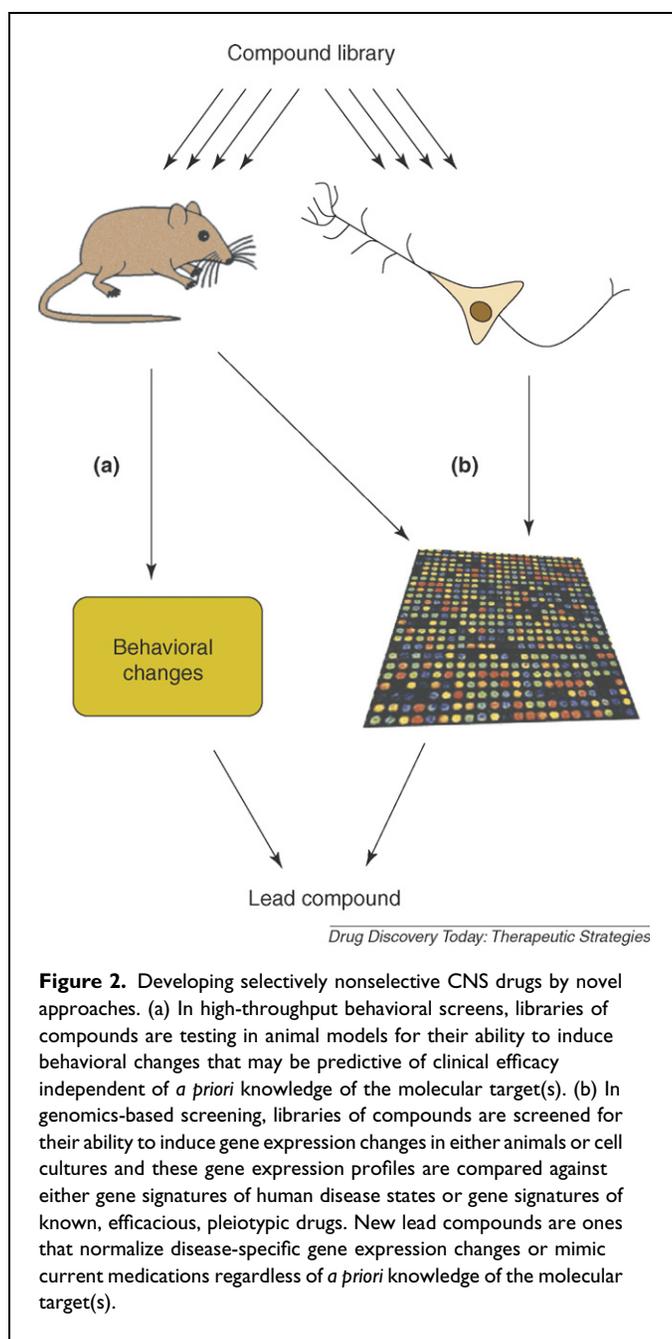
acting selectively at multiple targets simultaneously; so-called 'designed multiple ligands' [19]. The designed multiple ligand strategy involves combining PHARMACOPHORES (see glossary) from two or more selective ligands either by the addition of a linker to form a conjugate or by taking advantage of structural commonalities to overlap pharmacophores [19] (Fig. 1b). As an example of designed conjugated ligands, opioid ligands have been conjugated to form homodimeric ligands with increased potency at opioid receptors due to enhanced interaction with dimerized receptors [20]. Because homo- and heterodimerization are known to occur between many brain receptors [21], it is conceivable that conjugated multiple ligands could be designed that interact selectively at heterodimeric signaling complexes.

Overlapping pharmacophores, however, has more promise in CNS drug development because of the high degree of structural similarity among both potential molecular targets and their ligands. This structural similarity is also a major disadvantage because designing drugs capable of targeting only a subset of similar molecules is exceedingly difficult. Interestingly, though, success at creating a designed multiple ligand that interacts with two very dissimilar receptor super-families has recently been achieved [22]. Using the structural similarities between fluoxetine and the acetylcholinesterase inhibitor rivastigmine (Novartis, <http://www.novartis.com/>), a combination drug was designed that maintains high affinity for both targets and could be a useful treatment in Alzheimer's disease [22].

Although designed multiple ligands facilitate the rational development of drugs that target multiple receptors, this approach has some serious disadvantages. For example, molecular weights can become large leading to unsuitable pharmacokinetics. In addition, it is difficult to attain balanced activity at each target. As such, although designed multiple ligands may lead to a few successful CNS drugs, this approach is unlikely to provide medications superior to the current armamentarium.

High-throughput behavioral screening

Animal models have played a large role in drug discovery for much of the past century, often in the first-line screening of new compounds. For example, amphetamine-induced locomotor hyperactivity in rats has been widely used to test new compounds for antipsychotic activity [23], although, because compounds must significantly block subcortical dopamine receptors to have an effect in this model, compounds with low D₂-dopamine receptor affinity may be missed. Other models that could be used for behaviorally based screening of 'magic shotguns' include suppression of conditioned avoidance responding and normalization of disrupted prepulse inhibition. Because CNS drug discovery differs from most other therapeutic areas because of the complexity of CNS disorders, high-throughput behavioral assays might be



useful for the identification of novel medications for diseases such as depression and schizophrenia [1,24].

The difficulty comes, however, in finding animal behavioral models with good predictive value. Currently available pre-clinical models for antipsychotics are generally good at predicting atypicality (i.e. efficacy in the absence of EXTRAPYRAMIDAL SIDE EFFECTS, see glossary) but are ineffective at predicting overall efficacy. Similarly, available pre-clinical models for depression are fairly adequate at predicting clinical efficacy, yet are relatively ineffective at predicting the speed of action and the overall efficacy relative to standard comparators. For example, novel antidepressants with potentially greater efficacy (i.e. NMDA antagonists [25] and glucocorticoid

antagonists [26]) might not be reliably predicted by current pre-clinical tests to be effective. This suggests the need for continued development of newer animal models of disease.

To successfully use behavioral approaches to screen extensive compound libraries, highly automated high-throughput behavioral systems will need to be developed that measure a wide range of behavioral parameters rapidly [27] (Fig. 2a). In fact, at least two novel antidepressants currently in early-phase trials, YKP10A (Janssen Pharmaceuticals, <http://www.janssen.com/>) [28] and nemifitide (Tetragenex Pharmaceuticals, <http://www.innapharma.com/>) [29], were discovered using this type of approach. Interestingly, neither drug seems to have any appreciable affinity for any known antidepressant drug target [28]. These results highlight the potential of large-scale, automated behavioral screening of compound libraries for discovering drugs with novel mechanisms of action and possibly improved efficacy. The obvious advantage to a behavioral approach is that responses are examined in entire organisms rather than in simplified experimental systems.

Genomics-based screening

A promising approach for developing selectively nonselective drugs for CNS diseases is one in which compounds are screened on a genomic basis. That is, drug candidates could be screened according to their ability to alter the expression of multiple genes and gene families (Fig. 2b). In this approach, compounds with known efficacy and pleiotypic actions can be screened both *in vivo* and *in vitro* for their effects on gene expression, creating a gene expression 'signature.' Once these signatures are identified, libraries of small molecules can be screened to discover compounds that yield similar signatures.

Atypical antipsychotics such as clozapine are particularly excellent candidates for generating drug signatures because they have known beneficial effects, although the exact mechanisms responsible for their efficacies remain unknown. If patterns in the alteration of gene expression could be identified within a family of drugs, this information could then be used to identify novel compounds that similarly alter gene expression. Alternatively, once disease-specific signatures are identified, compounds could be screened for their ability to change gene expression in the opposite direction. These novel compounds can then be optimized by medicinal chemistry techniques to improve therapeutic profile and to eliminate interactions with potentially toxic molecular targets (for example, the 5-HT_{2B} receptor and valvular heart disease [30] and H₁ histamine receptors and weight gain [31]).

There are significant advantages to the genomics strategy, most notably being an unbiased, genome-wide approach that does not rely on known targets. This approach circumvents the concern that adequate treatments cannot be developed for major mental illnesses because the underlying causes

remain incompletely understood, because it does not rely on *a priori* knowledge or assumptions. Theoretically, drugs that normalize genes that are altered in diseases such as schizophrenia could better address the underlying causes of disease. There are, however, significant hurdles to overcome for a genomics-based approach to be successful. For instance, post-mortem brain samples from persons with schizophrenia cannot be considered a pure source of a disease-specific gene expression signature, as it is likely that such persons were chronically treated with antipsychotic drugs. Likewise, cultures of neuronal cells cannot fully represent the neural networks of the intact brain and thus alterations in gene expression from drug administration *in vitro* is not likely to fully correlate with *in vivo* changes. Nevertheless, a genomics-based approach to drug discovery will likely yield novel insights into disease processes and mechanisms of drug action and has great potential to lead to novel medications for CNS disorders.

Conclusions

There have been enormous advances in our understanding of the basic biological processes that contribute to human disorders, although a detailed understanding of the processes underlying complex CNS diseases remains elusive. With the sequencing of the human genome [32], there are unprecedented opportunities for gaining fundamental new insights into these complex diseases. Indeed, a major critique of current drug discovery approaches is that adequate treatments cannot be developed because the underlying causes of major mental illnesses remain incompletely understood. Although an enhanced understanding of the genetic basis of diseases such as schizophrenia will probably reveal validated molecular targets for drug discovery [33], it has become clear that a single target-based approach is not ideal for developing drugs for complex CNS disorders [1]. Thus, the systematic development of drugs that may address the root cause of disease, before our full understanding of those causes, will require novel screening approaches that look at whole organisms or systems. Behavioral- and genomics-based approaches provide great potential for the development of drugs with superior efficacy and side effect profiles for complex, polygenic CNS disorders.

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