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REVIEW

Models for depression in drug screening and preclinical studies: Future directions

Franco Borsini

Franco Borsini, Central and Peripheral Nervous System and General Pharmacology Area - R&D, Sigma-tau SpA, Socio Unico, Via Pontina Km 30400, 00040 Pomezia, Italy
Author contributions: Borsini F solely contributed to this paper.
Correspondence to: Franco Borsini, Central and Peripheral Nervous System and General Pharmacology Area - R&D, Sigma-tau SpA, Socio Unico, Via Pontina Km 30400, 00040 Pomezia, Italy. franco.borsini@sigma-tau.it
Telephone: +39-6-91393325 Fax: +39-6-91393988
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Abstract

The basic consideration in the field of antidepressants is that tests to model depression do not exist, as depression etiopathology is unknown. So far, any kind of proposed model for depression needs to satisfy construct, face and predictive validities. In the present editorial, this idea is challenged, based on the fact that "old" methods can only reveal therapeutical "me-too" drugs and that there is no longer a need of therapeutical "me-too" drugs in the field of antidepressants. Since reduction in the number of antidepressant non-responders is a real medical need, the predictive validity of animal models will be challenged in the future, as the new methods should be based on antidepressant-insensitive animals. Moreover, antidepressants exert similar effects in depressed and non-depressed subjects, but mood normalization is only induced in depressed patients. This implies that the use of normal cells and animals only involves pharmacological rather than therapeutical actions of drugs. Therefore, the use of environmental-induced changes, in the hope that these can evidence antidepressant-insensitive animals, will predominantly be used in the future. In the choice of experimental settings, other factors need to be taken into consideration: (1) gender of animals, as depression affects females more than males, (2) natural rhythmicity in drug effects; (3) pharmacokinetics; and (4) possible biomarker(s) to be measured. There are no golden recipes to discover new antidepressants but the experimental long-term strategy should very clearly be declared before starting the experiments.

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Key words: Antidepressants; Animal models; Biomarkers; Predictive validity; Stress; Gender; Variability

Peer reviewer: Rajkumar Ramamoorthy, Postdoctoral Fellow, PhD, Department of Pharmacology, Yong Loo Ling School of Medicine, Neurobiology and Ageing Programme, Level 4, Centre for Life Sciences, 28 Medical Drive, National University of Singapore, Singapore 117456, Singapore

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PREMISE

Despite the many results published on various mechanisms of action elicited by various compounds or herbal extracts in preclinical settings, which might suggest new potential antidepressant actions, well-established therapeutical antidepressant activity of drugs only derives from placebo-controlled, double-blind, randomized clinical phase Ⅲ results. Such clinical results also need to include long-term antidepressant benefit, where efficacy is also retained during maintenance treatment. Based on the efficacy of short- and long-term clinical phase Ⅲ trials, regulatory authorities give the authorization to commercialize the new medicine. There are several marketed antidepressants: i.e. tricyclics, monoamino-oxidase inhibitors and selective or mixed monoamine (serotonin, noradrenaline or/and dopamine) reuptake inhibitors.

The richness of such armamentarium is very important because physicians may choose a particular drug with a more tolerable profile for a particular patient, above all when severe comorbidity is present. Electroshock therapy is also considered to treat depression[1], mainly in drug-resistance cases[2]. In this editorial, only those drugs with approved labeling as antidepressants will be considered as efficacious medicines. In fact, some compounds that had shown some efficacy in preclinical and early clinical studies may not confirm their activity in larger clinical trials, or have been in clinical studies for too long, casting some doubts on their therapeutical benefit and/or safety window, as in the case of NK-1 (TAK-637; L733060[3]; MK869[4] or GR (mifeprisone), CRH1 (R121919; ORG34517; and NBI34041, SB723620), V1b (SSR149415) antagonists[3]. So, despite the initial scientific excitement, no compound that interferes with the stress system and that showed antidepressant-like activity in animals, exerted consistent antidepressant activity in humans[3]. Furthermore, the 5-HT$_{1A}$ receptor agonists gepirone, ipsapirone, flesinoxan and flibanserin[3,5-8], the peptide analog of melanocyte-inhibiting factor nemifitide[9] or the triple monoamine uptake inhibitor NS2359, as reported in the NeuroSearch web site[10], never reached the market or showed satisfactory antidepressant activity in clinical trials. Moreover, no herbal medicines have been registered as antidepressants. This does not mean that such compounds may not be useful for a particular subpopulation of depressed subjects but, until their efficacy is clearly shown and approved for that particular subpopulation, they are not considered as efficacious antidepressants. This "rigid" way of thinking is only dictated for the sake of clarity and for the scope of the present editorial, i.e. stimulating the search for new therapeutical strategies. What is written in the present editorial only represents personal points of view that may or may not be shared by the reader. Furthermore, as most recent publications often offer a complete overview of the literature, such papers will be quoted rather than the most well-known articles. In DOIng this, there is absolutely no intention to underestimate the very important contribution of some researchers who were pioneers in their field.

BACKGROUND

The field of antidepressants has been characterized by the introduction of more selective and potent medicine[11] into the market, with different side-effects than older antidepressants[12]. However, even if some drugs appear to be therapeutically better than others, it is not established that the new antidepressants have improved the number of responders or remitters better than the older medicines[13], the number of responders and remitters is an important medical need in the field of unipolar depression[14]. Several scientists have tried to analyze the reasons of such research difficulties in drug discovery. Animal models, incapability of detecting patient subpopulations, clinical trial design, unsatisfactory medical end-points, lack of biomarkers, psychological pressure on scientists working in pharmaceutical industries, marketing strategies and difficulty in establishing public-private R&D partnership have, from time to time, been evoked as causes for such failures[15-21]. However, such failure in drug discovery is not a peculiar aspect in the field of antidepressants or drugs for the central nervous system (CNS) as it also happens in other therapeutical areas other than the CNS[22]. More recently, genetic polymorphism has also been implicated in depression and in reduced antidepressant response in patients[23,24]. Various attempts have also been made to better define the role of neuroimaging for both drug-treatment and depressive patients[25-30]. Likewise, some biomarkers have also been suggested to differentiate drug-sensitive from drug-resistant patients[2]. Despite the interesting premises of genetic and neuroimaging findings or of various biomarkers, there is no universally agreed consensus on such indicators for antidepressant-resistance or for the course of the mental illness[1,31]. However, the real reason is that the etiopathogenesis of mood disorders is unknown and modeling what it is unknown is a challenging task; of course, this also applies for other pathologies. Thus, active searching for important biological indicators of antidepressant-resistance and of depression as mental illness seems to be the only way to proceed in this field.

A further difficulty in the field of antidepressants (but not only in this therapeutical class) is that the results of potential antidepressants in clinical trials are not always published[13]. Therefore, whether the failure is due to weak antidepressant activity or other causes (metabolism, side-effects, high placebo response, depressed sub-population, loss of interest by the company, *etc.*) is difficult to ascertain. A further complexity is that antidepressants are used, not only to normalize depressed mood, but also to treat anxiety disorders[32] and chronic pain[33]. Thus, it appears that antidepressants induce different therapeutical effects and to dissect these in different mechanisms of action is complex.

The present editorial does not review animal models or list mechanisms of action that are involved in pharmacological effects of various potential antidepressants, as manuscripts on these topics already exist[18,34-52]. The aim of this editorial is to express a personal point of view, based upon many years of experience, in order to elicit the interest of researchers and let them think about how they use their methodologies. In fact, failure to discover new antidepressants may not solely depend on chosen animal models or preclinical settings but also on how these preclinical methods are used.

As aforementioned, the medical needs in the field of antidepressants are, among others[53], an increase in response and remission rates[14] and to shorten therapeutical onset of action[54,55]. Nevertheless, very few attempts have been made in preclinical settings towards these directions. Thus, current preclinical models to screen potential antidepressants are vitiated by a tautology, as a model is only validated with already known clinically effective drugs.

Since it is difficult to think that new antidepressants may emerge with old methods, the chance to find innovative antidepressants is uniquely based on clinical trials. Researchers should take the courage to embark in alternative experimental strategies. This manuscript deals with this point of view.

BEHAVIORAL STATUS OF ANIMALS

Therapeutically, antidepressants normalize impaired mood function in depressed patients and only induce other (and/or adverse) effects in non-depressed subjects[55-57]. In accord with these findings, and in contrast with what is reported for depressed patients, in healthy subjects monoamine depletion does not change mood parameters[58] and antidepressants, in general, do not seem to modulate mood[59,60]. In healthy volunteers, antidepressants may exert pharmacological effects[61,62] that are similar to those observed in depressed subjects[63]. Thus, the use of normal animals does not seem appropriate for studying the mechanism of "therapeutical" actions of antidepressants. Nevertheless, antidepressants are often given to animals that are considered "normal" and reviews are written by using these data[38,64,65]. The first question is whether antidepressant-induced effects in normal animals may be considered as epiphenomena. Unless it becomes clear that "depressive" subjects have impairment in the function that is restored by antidepressants, the effects in normal animals may be related to the pharmacology of antidepressants rather than to their antidepressive therapeutical properties. This means that, from a therapeutical standpoint, all the results coming from normal animals or *in-vitro* assays from unaltered biological systems are questionable.

Only animals with "altered" biological systems should be used to investigate potential antidepressants; therefore, how to define a biological system as "altered" is important. Only a portion of human subjects develop depression. Thus, those procedures that induce "depression-like" effects in all animals should be avoided. Moreover, antidepressants only partially work clinically. Therefore, only those procedures which allow distinguishing antidepressant-sensitive and antidepressant-insensitive animals should be considered. This leads to another issue, in which animals can be considered as "real" controls. If normal animals serve as control for "altered" animals, in "altered" animals the comparison should be made between antidepressant sensitive and insensitive subjects. Thus, the new potential antidepressant should be tested in antidepressant insensitive animals. Consequently, one of the principles considered important for animal models, the predictive validity, will not be verified anymore.

As a diagnosis of depression is based on interviews, whether the "alterations" provoked in animals are related to human depression is difficult to determine. Nevertheless, antidepressants should be administered after the behavioral changes and not before[66]. This difference may discriminate between antidepressant- and anxiolytic-like effects. Such a concept derives from the fact that some anxiety disorders, such as generalized anxiety, compulsive-obsessive disorders or panic attacks, may be more related to the difficulty of coping with stressful situations rather than feeling despair or anhedonic. However, this concept does not apply to post-traumatic stress disorder (PTSD), where there is a clear traumatic precipitating event. In PTSD, subjects undergo an intense acute stress. Thus, it may be that the use of repeated stressful procedures might be helpful in determining potential antidepressant properties. That chronic stress, which lasts for weeks or months, is a more of a reliable predictor for depressive symptoms than acute has already been suggested[67,68]. Among the various behavioral methods used to detect potential antidepressant activity, some of them, such as learned helplessness, chronic mild stress and competition within a social milieu, seem more promising than others because they are based on repeated stressful conditions[18].

How the test is carried out is an important factor. Learned helplessness, for example, may be provoked by using stress levels that induce failures in the escaping behavior in all animals[69] or only in part of them[70,71]. However, some animals do not develop helplessness, as shown by the fact that it is possible to genetically divide those who develop helpless from those who do not[48,72-74]. Within the frame of competition within a social milieu, the resident-intruder paradigm[42,75-78] and pair-animals forced to feed in a limited time[38,78,79] are interesting, because not all animals develop the same reaction to the stimuli. Furthermore, rodents can be divided in to antidepressant -sensitive and -insensitive animals[39,54,79].

Other animal paradigms that are commonly used, such as the forced swimming test, the tail suspension test, maternal separation, olfactory bulbectomy and operant responses, appear more problematic in the sense that all the animals apparently develop similar behavioral changes and the stress is not delivered chronically, except for bulbectomy where rats may be lesioned from the very beginning[18].

READ-OUTS

The issue is not to reproduce the same symptomatology of depressed subjects in animals, but to interpret the animal behavior. For example, in the learned helplessness procedure, there is discussion whether it is better to consider as read-out the so-called "fixed ratio 1" or FR1, the escape from the compartment where there is the electrical shock to another one devoid of danger[80-83], or the so-called "fixed ratio 2" or FR2, which requires passing through the doorway twice in order to turn off the shock[84-86]. FR2 should better reproduce the wish to avoid a frustrating situation, whereas FR1 seems more difficult to interpret[87,88], even if it is easier to obtain.

Anhedonia, namely lack of pleasure, is a frequent symptom in depressed patients. Typically, in animals, anhedonia is assessed by measuring intracranial electric self-stimulation or sucrose-intake in chronic stressed ani-

mals[18]. Despite the fact that not all the stressed animals reduce their intake of a sweet solution[88], it seems that the reduction in sucrose-intake may not only depend on reduced motivation[77,89]. This point deserves further critical discussion[90].

Interestingly, young animals seem to be resistant to chronic mild stress-induced anhedonia in contrast to adult rats[91], indicating an age-dependant effect of chronic stress.

All read-outs are based on animal movements, such as escaping, swimming, consummatory behavior, aggressiveness and vocalization. Generally, researchers measure "normal" motor activity to support the notion that the observed effects do not depend on changes in capability to move. This experimental procedure may induce misleading interpretation. Animals may have normal motor activity but can change it depending on the test procedure used. For example, flibanserin, a potential antidepressant that did not match the expected outcome in clinical trials[3], reduced spontaneous motor activity in rats[92] but did not change, even at a higher dose, swimming speed in the Morris water maze[92] or inter trial crossings in the learned helplessness test[93]. Flibanserin reduced motor activity in the light-dark test in mice[92] but did not change it in an open-field, even at a higher dose[94]. However, how changes in motor activity may affect the behavior in so-called animal models for depression is difficult to ascertain, as a compound's effect may be test-dependent[92]. So, the effects on motor activity should be interpreted with caution in the therapeutical sense.

As aforementioned, when the results of a new compound are presented, information on its pharmacokinetic/metabolic profile should always be provided, together with its effects on gross animal behavior[95,96].

Differential responses of both sexes to antidepressants should also be taken into account. This has already been reported in the pharmacokinetics and pharmacodynamics (time to response, efficacy and side effects) of antidepressants in depressed patients[97,98]. In animals, Dalla *et al*[99] reviewed this field and concluded that females are more sensitive than males in the chronic mild stress and forced swimming test[100], but they are not as susceptible as males in the learned helplessness model. Sex differences may also be observed in Flinders rats, not only for their serotonergic tone, but also in response to antidepressants, as these drugs tend to alleviate sex differences[99]. Immunomodulation, neurochemical and behavioral responses point to the important role of the immune system in the pathophysiology of depression[99,101,102] and it is possible that the actions of estrogens in the brain may affect the serotonergic system in a sexually dimorphic manner[100]. Pharmacokinetics/metabolic profile between sexes should, however, always be considered before reaching a conclusion on sexual dimorphism[103].

Another aspect to consider is the possible biological rhythmicity in the animal's behavior and/or drug effect[104-112]. On the other hand, this phenomenon has also been observed in antidepressant-treated patients[113]. Thus, to be sure that the read-outs are consistent and reproducible, experiments should be repeated throughout the year and in both males and females. For example, by using the forced swimming test, DBA/2 mice were reported to be sensitive[114,115] or insensitive[116,117] to selective serotonin reuptake inhibitors. Whether these contrasting results were due to testing in different periods of the year still remains to be elucidated. Similar considerations hold for the strain C57BL mice in the tail suspension test, where it was found that they were highly citalopram-sensitive[118] or almost citalopram-insensitive[119].

TRANSLATIONAL MEDICINE

Animal models may serve to provide some information on the possible therapeutical usefulness of new compounds. Once a Pharma Company is convinced to proceed in clinic with a compound, it is necessary to be sure that the administered dose in humans is the appropriate one. Clinical phase I gives information on tolerability and pharmacokinetics/metabolic profile of the new medicine in healthy volunteers. Clinical phase Ⅱ is aimed at evaluating the therapeutic benefit of the new drug in patients. The problem is how to be sure that the drug plasma levels guarantee the desired pharmacological/therapeutical action in depressed subjects, above all if comorbidity or pathologies that may interfere with metabolism of the compound are present (i.e. renal or hepatic malfunctioning). With the lack of biomarker(s), clinical trials are run without any idea about the goodness of the dose. Thus, whether a clinical trial failed because of no satisfactory clinical outcome or for other reasons is often unknown. The biological marker(s) should be checked in ill subjects and not in healthy volunteers. In fact, neurotransmitter brain concentrations or receptor function status may change in the pathological brain[120-124] and, therefore, an image of the brain or other parameters in healthy volunteers may not provide the right information.

Despite the high interest elicited by brain-derived neurotrophic factor (BDNF), which is decreased in serum and leucocytes of depressed patients prior to antidepressant treatment and increased after 12 wk of escitalopram administrations[125], BDNF was also found to be increased in other neuropsychiatric disorders, such as schizophrenia, panic disorder, eating disorders, Alzheimer's and Huntington's disease[126]. Thus, BDNF may be an indicator of some brain vulnerability rather a specific biomarker for depression and antidepressant-sensitivity. Additionally, there is no apparent correlation between BDNF changes and depressive symptoms[127]. Moreover, BDNF is also increased by amitriptyline in whole blood cell culture from volunteers who are healthy and not ill[128]. The analysis of this biomarker is made more difficult, because the effect of the stress on this parameter in animals is age-dependent[91]. Nevertheless, there are many suggestions of possible biomarkers derived from depressed patients[129-134] or "altered" animals[3,135-137], but

so far none of them has completely been recognized as indicative of depression. Of course, this does not hamper having a biomarker that could be useful to assess the pharmacological, not necessarily the therapeutical, activity of the new medicine.

As far as "pharmacological" activity is concerned, there are no well documented reports. However, the interested reader should read the two very recent reviews on this topic: Leuchter *et al*[138] and Ward *et al*[139]. The first one describes what is interesting in examining the structure and function of the brain and genomic, proteomes and metabolomic measures. In contrast, Ward and Irazoqui[138] focused their attention on what antidepressants do not control or cure depressive symptoms. However, as one can see, none of them have the right to be conclusive.

CONCLUSION

The current available models are simply experimental paradigms sensitive to current antidepressants, which were initially discovered by serendipity. While the scientific information on the pharmacological mechanism(s) of action of antidepressants is always important, the strategy to find therapeutically valid antidepressants must drastically change. Since the first animal models were proposed, there has been intense discussion about the criteria that models should have to be considered as suitable animal models[49]. However, despite this, all animal models are generally equally used and preference is given to those that are easier to be performed.

The current methodology has permitted discovery of the mechanism(s) of action of existing antidepressants, such as monoamine uptake blockade and monoamino oxidase inhibition. The methods used so far might also be useful to study how to reduce the therapeutic delay in treating depression[93,139], even if there is clinical difficulty in assessing fast antidepressant action. However, the weaknesses of the actual way of working in the field of antidepressants appear clear. Whereas on the one hand, "altered" animals are used as behavioral models to test the antidepressant-like potential, on the other hand, normal animals are generally used to evaluate neurochemical, electrophysiological, biochemical and molecular mechanism(s) of action of known antidepressants. Moreover, susceptible animals may be used in behavioral studies, whereas all the animals are used in non-behavioral experiments. Thus, there are two variables: "alteration" *vs* "normality" status, and "susceptible" *vs* "all" animals. Therefore, to reconcile all the results in order to formulate a working hypothesis is really a tough job.

The rationale should be based theoretically on the background knowledge and then verified in antidepressant-insensitive animals for that particular model. The construction of a theoretical hypothesis is essential to have an idea of possible biomarkers or their surrogates. Entering clinical phases without having biological marker(s) to investigate, in order to assess whether compound plasma levels may be sufficient to trigger the desired pharmacological/therapeutical effects, seems to be destined to fail.

As previously written, it is difficult to model what is unknown. However, there are already some published behavioral approaches that seem more promising than others. One has recently been published by Carboni *et al*[135], using Flinders rats. As expected, the immobility time in the forced swimming test of the rats belonging to the Flinders Sensitive Line (FSL) was higher than those belonging to the Flinders Resistant Line. Both the antidepressants escitalopram and nortriptyline decreased immobility time in "normal" FSL rats, but not in FSL rats that underwent repeated maternal separation at postnatal age. This appears to be an example on how a behavioral manipulation makes animals resistant to drug treatment. Moreover, gene-environment interactions revealed changes in peripheral levels of analytes that are involved in inflammation and the regulation of metabolic pathways.

Prediction of clinical efficacy of new antidepressant compounds is not easy and needs a very high level of expertise. The process for potential innovative antidepressants should go through the following steps: (1) have a clear "construct" criterion; (2) selection of antidepressant-insensitive animals by using "old" methods (i.e. escape deficits in the learned helplessness test; sucrose intake in the chronic mild stress; social defeat); (3) to test the compounds after and not before behavioral "alterations"; (4) to verify that insensitivity does not depend on biological rhythms or pharmacokinetics/metabolic profile; (5) to use both females and males; and (6) to identify biomarker(s). If such a procedure is not followed, another therapeutical me-too antidepressant is certain to be found.

In order to discover the antidepressant of the future, the problem of non-responders needs to be addressed. It is also necessary to take into consideration that it is difficult to have a unique animal model for depression, as all pieces of evidence "argue against a unified hypothesis of depression"[101]. Experimentally, it means that all antidepressant-sensitive animals should be discarded[140]. Thus, the alternative is the use of behavioral methods to identify antidepressant-insensitive animals and electrophysiological, neurochemical, biochemical and molecular studies should be performed in these animals. *In-vitro* studies should also be performed by using cells from "altered" animals. In this way, the concept of predictive validity cannot be applied for future research anymore.

The definition of "antidepressant-insensitive" should depend on scientifically-based evidence. Thus, one should be sure that the insensitivity does not depend on pharmacokinetic/metabolic profile of the drug or particular seasonal effects. This implies replication of a particular test throughout the year with concomitant plasma level assay. However, nobody has the golden recipe to discover original antidepressants, but after 50 years, where only me-too antidepressants in the therapeutical sense were introduced in the market, it is time to change. The first

change should be to not use any more normal animals or normal cells. For example, there is a wonderful review on the effects on brain dopamine after antidepressant and drug treatment in normal animals[38]. However, whether such a review may increase the insight in the therapeutical effects of antidepressants is questionable, even if the hypothesis that the authors put forward on dopamine D_1 receptors is fascinating. In fact, almost all data refer to normal animals. Thus, the hypothesis that antidepressants may enhance dopaminergic D_1 sensitivity should be supported by data originated in "altered" animals.

Finally, the problem is how to screen for new antidepressants. Of course, the experiments should be randomized and the observations performed by observers who are unaware of the treatment. The question is whether it is worth spending such a long time for such a process. It is personal opinion of the author of this editorial that it is necessary, if we want to embark a new era in the field of antidepressants.

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