Chapter

Introductory Chapter: Antidepressants - Preclinical, Clinical and Translational Aspects

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1. Introduction

In 2011 two extensive studies were published about prevalence and associated disability, including the associated disease burden and financial costs, of brain diseases in Europe [1–3]. A shocking finding was that in a European population of more than 400 million people, approximately one-third suffered from a psychiatric or neurological disorder. In the psychiatric disorders, anxiety disorders had the highest 12-month prevalence (14%) and depression (7%), approximately 61.5 million people. The disability burden of psychiatric diseases including major depression is tremendous being defined in disability-adjusted life years (DALYs). In 2010, more than 26% of all cumulated disease burden in Europe was due to brain disorders; depression belongs to the top diseases with the highest DALYs. Major depression is a severe brain disorder associated with long-term disability and low quality of life. Suicide and suicidal attempts are highly associated with depression and have an enormous impact on relatives and society.

2. Antidepressants

Since the 1950s and 1960s of the last century, discovery and development of antidepressants have gradually emerged. Early antidepressants like imipramine and the irreversible monoamine oxidase inhibitors (MAOI) were discovered by serendipity. These "accidental" discoveries have led to intensive research and have led to a series of new antidepressants, like the tricyclic class (TCA, e.g., imipramine, nortriptyline, amitriptyline, and clomipramine) and a series of (both reversible and irreversible) MAOIs. These antidepressants, although still clinically available, are not anymore first-line medicines, mainly because of their sometimes severe side effects. The research in the 1960s and 1970s led to the insight that TCAs block monoamine transporters (reuptake carriers) for serotonin and noradrenaline to varying extent. Some TCAs are preferential serotonin transporter (SERT) blockers (clomipramine, amitriptyline), while others are preferential noradrenaline transporter (NET) blockers (desipramine, maprotiline) or mixed SERT/NET blockers (doxepin, imipramine). TCAs also block several neurotransmitter receptors, particularly muscarinic cholinergic, H_1 histaminergic, and α_1-adrenoceptors, which is mainly responsible for their (unwanted) side effects, including sedation, dry mouth, and constipation.

Based on the early, but overly simplistic hypothesis that low serotonin and/or noradrenalin levels/activity in the brain are associated (or even causative in) with

depression, the development of selective serotonin reuptake inhibitors (SSRIs; fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram) and selective noradrenaline reuptake inhibitors (NRIs; reboxetine, atomoxetine) and mixed 5-HT/NA reuptake blockers (SNRIs: venlafaxine, duloxetine) was enabled. Several other antidepressants have been developed (e.g., bupropion, mirtazapine, agomelatine, trazodone, nefazodone), with variable mechanisms of action. In general, SSRIs are the drugs of choice and first-line in the treatment of major depression [4]. The first SSRIs (zimeldine, fluvoxamine) were introduced in the early 1980s [5], and in the ensuing decade, several followed (fluoxetine, paroxetine, sertraline). Up to this moment, SSRIs still are first-line medication in MDD, but some breakthrough antidepressants are emerging (esketamine), whereas extensive and intensive research and development are ongoing [6].

3. Antidepressants: how good are they?

SSRIs like all antidepressants come with associated problems, viz., (1) side effects, (2) limited efficacy, and (3) slow onset of action.

3.1 Side effects

Major depressive disorder (MDD) typically comes in recurrent depressive episodes rather than a single episode. Antidepressant treatment requires to focus on both acute and maintenance aspects of MDD. The primary goal of the acute treatment phase (8–12 weeks) is to achieve symptomatic remission. In the acute phase, emerging side effects of the first-line treatment (often an SSRI) and the tolerance development of the patient strongly co-determine a positive antidepressant response to SSRIs or SNRIs. Main side effects (occurring in approximately 10–30% of patients) are nausea, dry mouth, sweating, sexual dysfunction, somnolence, nervousness, anxiety, dizziness, and insomnia [7]. If SSRI/SNRI treatment is not effective, MAO inhibitors or TCAs (as third-line treatments) may be used, although they come with additional and often more severe side effects. Second-line treatment includes novel antidepressants like vilazodone or vortioxetine or second-generation antidepressants like agomelatine, bupropion, or mirtazapine. All have their own side effect profile and are comparably effective antidepressant compared to SSRIs and others [8]. Lifetime major depression has high psychiatric comorbidity with anxiety disorders, substance use disorders, and impulse control disorders. Many depressed patients have medical (physical) comorbidities requiring pharmacotherapy, and this brings the risk of drug-drug interactions, often associated with cytochrome (CYP) P450 or P-glycoprotein-mediated effects. This may exacerbate side effects of drugs or interfere with the pharmacological action.

The most disturbing side effects of SSRIs and some TCAs (e.g., clomipramine) are those on sexual functioning like libido, orgasm, and arousal problems. In contrast to some other side effects that are prominent in the first phase of treatment, but often diminish upon drug continuation (like nausea and dizziness), sexual side effects do not disappear and are often causing drug discontinuation. MDD itself is already associated with 50–70% enhanced risk of sexual dysfunction (SD), and prescribing antidepressants with inherent effects on sexual behavior strongly enhances the risk for noncompliance or discontinued drug-taking [9]. Such a scenario can be avoided by prescribing (e.g., as second-line choice) antidepressants without (or less) sexual side effects (e.g., agomelatine, bupropion, vilazodone, or vortioxetine). Because depression occurs during all life phases, it is also common during pregnancy with an estimation of 20% of women that experience depressive

symptoms during that time [10], whereas around 4–8% of pregnant women suffer from MDD. Depression of the mother impacts the fetus, e.g., by the enhanced cortisol levels in the mother which also pass the placenta. There is strong evidence that increased stress levels of the mother may lead to neurological and behavioral changes in the child which persists at least into adolescence (e.g., [11]). In the contribution of Staal and Olivier (Chapter 2), a review is given of the consequences of depression during pregnancy. Although the consequences for a child, adolescent, or adult that was in utero subject to a mother experiencing MDD are not yet completely clear, the first results point to a negative influence [12]. However, nowadays a considerable number (2–3%) of pregnant women with MDD are treated with antidepressants, mostly with SSRIs. SSRIs cross the placenta and reach the fetus, including the central nervous system. Because serotonin plays a key role in embryonic development as a neurotrophic factor, disturbances in its level might lead to (permanent) changes in the offspring [13–15]. Chapter 2 summarizes the state of the art of the interaction between untreated or SSRI-treated mothers with severe depression. It is not yet clear whether SSRI treatment or not is preferable for depression in pregnant women.

3.2 Limited efficacy

Antidepressants have limited efficacy in relieving depressive symptoms in MDD patients. It is estimated that approximately 50% of depressed patients are adequately treated by the available interventions, including pharmacotherapy [16]. Most patients receiving pharmacotherapy fail to achieve and sustain remission, eventually not leading to functional recovery. The majority of patients starting an antidepressant require several subsequent and different antidepressants or adjunctive therapy (either pharmacological or cognitive behavioral therapy). There is evidence that if a chosen treatment strategy (a certain antidepressant, often an SSRI) results in symptomatic improvement within the first weeks, full remission is likely, but the reverse is also true: lack of early improvement predicts a high chance on non-remittance [17]. After failure of a number of (adequately dosed) antidepressants of different classes (SSRI, TCA, MAOI), and augmentation with various drugs (e.g., antipsychotics) and other strategies (e.g., cognitive behavioral therapy), patients are considered treatment-resistant. Treatment-resistant depression (TRD) is defined as the failure to respond to one or more standard antidepressant treatment trials of adequate dosing and duration [18, 19]. TRD is a big challenge to treat. Although depression is diagnosed as a single entity, MDD [20] is an extremely heterogeneous disease [21] with regard to symptoms, etiologies, and pathophysiologies, with some moderately heritable background [22] and a high susceptibility to adverse life events [23]. TRD reflects a complex, heterogeneous state, probably with multiple causal underlying mechanisms. It is not clear how and where TRD patients differ from non-TRD patients, although early life stress seems to facilitate treatment resistance [24]. Research is clearly needed to establish the pathophysiology of TRD, the complex mechanisms involved, and the heterogeneity of the TRD patient. Unfortunately, depression is presently not a high priority for pharmaceutical companies, due to recent failures in antidepressant discovery and lack of understanding of the mechanisms involved and the consequent lack of available targets. Akil et al. [21] argue a need of a fundamental approach in the search for new and effective treatments for TRD. They propose to identify dysfunctional brain circuitry in animal models of depression, looking at changes in associated gene expression. Combination of animal research with human genetic and imaging studies must generate circuits and molecules that are both altered in the animal models of TRD and also in selected patient populations. Such translational and highly integrated research may lead to new targets for specific anti-TRD medication.

In Chapter 3 Marek and colleagues describe the research on orexin 2 receptor antagonists as putative new antidepressants. Orexin, a hypothalamic neuropeptide, is known for its involvement in sleep-wake cycling of all mammals, including man. Orexin 2 receptor antagonists produce antidepressant activity in animal tests sensitive for antidepressant activity, including the DRL-72 sec schedule of reinforcement, an advanced screen for antidepressants [25]. Both positive and negative preliminary human data are present on orexin 2 receptor antagonists in depression, but further studies are needed to answer whether this approach might lead to new antidepressants or may be also effective in treatment-resistant depression.

3.3 Slow onset of action

The current most widely prescribed antidepressants, SSRIs and SNRIs, but also TCAs and MAOIs and other antidepressants, have no acute onset of action but work (gradually) over a period of weeks to months. It is still largely unknown what underlying CNS mechanisms are involved in the slow onset of action of antidepressants. In the case of serotonergic antidepressants (SSRIs, SNRIs), a complex interaction between various 5-HT auto- and heteroreceptors as modulators of the SSRI-induced chronic increase in CNS serotonin plays a role [26]. Acute administration of SSRIs Inhibits somatodendritic 5-HT_{1A} autoreceptors leading to inhibition of firing activity of serotonergic neurons and consequently dampened release of 5-HT in the forebrain, which, in some not yet understood way, contributes to the slow onset of action of SSRIs [27]. Desensitization of 5-HT_{1A} autoreceptors after long-term administration might overcome the decrease in 5-HT release and subsequently would lead to high serotonin release [27]. Combining an SSRI and 5-HT_{1A}-receptor antagonist might create a fast onset of action mechanism for antidepressant activity. The lack of availability of clinically approved selective 5-HT_{1A} receptor antagonists led to studies using the mixed β-adrenoceptor/5-HT_{1A} receptor antagonist pindolol together with various SSRIs in MDD patients [28]. In a placebo-controlled study, pindolol increased the antidepressant efficacy of fluoxetine, although no significant improvement in onset of action of the combination was found [29]. Pindolol is probably not the best tool to perform this kind of "onset of action" studies (pindolol is a relatively weak and not a full 5-HT_{1A} receptor antagonist, and its beta-blocking activities induce side effects), but a study with a selective 5-HT_{1A}-receptor antagonist did not find any difference either. It was postulated [30, 31] that two new multi-target antidepressants, vilazodone (SSRI+ partial 5-HT_{1A} receptor agonist) and vortioxetine (SSRI+5-$HT_{1A,1B,1D,7}$ receptor agonist and 5-HT_3 receptor antagonist), might have an advantage over existing drugs in terms of efficacy and onset of antidepressant action, although clinical data thus far have not shown evidence for improving the onset of action [32, 33]. It is evident that antidepressants that primarily act via monoaminergic neurotransmission all share the slow onset of action principle, and new molecules stemming from this "classical" approach will not deliver fast onset of action compounds.

The finding that one single dose of intravenous ketamine produced rapid and sustained antidepressant effects in depressed patients led to a new and exciting opening in this field [34]. Ketamine, an NMDA receptor antagonist and dissociative anesthetic, produces at low doses mild dissociative and psychotomimetic effects but also exerted rather unexpected antidepressant effects. One single dose of ketamine (0.5 mg/kg, intravenously by slow infusion) induced a rapid antidepressant effect (within hours) that lasted for 7 days [35]. Later studies have confirmed the fast antidepressant onset, even in TRD patients [6]. However, notwithstanding the apparent breakthrough in fast treatment of depression, the side effects of ketamine are still troublesome for general use. Recently (March 2019) a nasal preparation of the (S)-enantiomer (esketamine) received FDA approval after successful phase 3 trials. Moreover,

new approaches for fast-onset and effective antidepressants via modulation of the glutamatergic-NMDA system are now subject of intense research efforts [6, 36]. One may expect a new range of novel antidepressants with as main attribute a fast onset of action. Whether these new molecules have a higher efficacy (>50% of responding patients) or accordingly lead to less treatment resistance has to be awaited. Moreover, the side effect profile is likely quite different from the classical "monoaminergic" antidepressants. Only large number of well-treated patients will unravel the impact of these side effects. If only the onset of action is improved, the acceptance of such a new antidepressant will strongly depend on its side effect and safety profile.

One of the big items in the research and discovery of new and innovative antidepressants is the availability of animal models that are able to measure "onset of action," "efficacy," and "side effects" [37]. Onset of antidepressant action in an animal model is quite difficult to assess. Most animal depression tests are acute, in that they respond immediately to a dose of a certain antidepressant, e.g., forced swim test, tail suspension test, or DRL-72 sec paradigm. Animal depression models that do not respond acutely but only after chronic treatment of the classic antidepressants are rather scarce, although indispensable in the onset of action discovery. One of such models is the olfactory bulbectomized (OBX) rat [37, 38]. OBX leads to stable and lasting changes in behavior after removing the olfactory bulbs [39]. OBX leads within days after ablation to permanent changes in activity, basal body temperature, heart rate and heart rate variability, and stress responsivity [39]. Increased locomotor activity in an open field is an often used simple parameter to measure the effects of antidepressants [38]. In an extensive review on available animal models, olfactory bulbectomy in rodents is considered superior to other animal models to detect onset of action of antidepressants [37], with a high sensitivity, specificity, and reliability and moderate ease to use the model. The model generated also the possibility to study effects of antidepressant treatment after cessation of treatment [40]. Chronic (14-day) treatment of imipramine (20 mg/kg) or escitalopram (5 and 10 mg/kg) in OBX and sham-operated rats led to reduction of the hyperactivity in an open field by imipramine and escitalopram of the OBX rats, without effects in the control rats. This reduction in hyperactivity of OBX rats induced by chronic administration of antidepressants remained after cessation of treatment and lasted for 10 weeks after imipramine and 6 weeks after escitalopram cessation [40]. We concluded that the OBX-induced changes in the brain state (neuroplasticity) are probably attenuated by chronic antidepressant administration and that these changes are only slowly returning to the previous OBX state. Pramipexole, a dopamine D3/D2 receptor agonist, used to treat Parkinson patients with additional antidepressant activity [41], indeed exerted antidepressant activity in the OBX model [42]. Pramipexole is also a psychostimulant and induces at higher doses enhanced locomotion itself, thereby interfering with the already enhanced activity of OBX rats. Remarkably, 1 week after cessation of treatment, pramipexole-treated OBX animals still were not hyperactive, similar to imipramine, thereby suggesting that antidepressant effects of drugs can be detected in the OBX model by using this post-cessation antidepressant-like effect [42]. Unpublished studies [43] found that 3- and 7-day treatment with imipramine (10 mg/kg/day) normalized OBX-induced hyperactivity in the open field. One week after cessation of imipramine treatment, hyperactivity returned, suggesting that longer periods of treatment (14 days) are at least needed to lead to changes in brain neuroplasticity underlying the suppression of OBX-induced behavioral changes. In a complicated experimental design, ketamine (10 mg/kg, IP) was given to OBX and control rats 24 hours before testing in an open field but appeared ineffective [44]. The experimental design did not give a clear cue about the onset of action of antidepressant activity of ketamine, and more directed research into this avenue has to be initiated. Pandey et al. [45] found that

14-day but not 7-day treatment with ketamine (1 mg/kg/day) reduced hyperactivity induced by olfactory bulbectomy, although combination of escitalopram (10 mg/kg/day) and ketamine (1 mg/kg/day) reduced hyperactivity at both 7 and 14 days. This may be an indication that ketamine in combination with an SSRI may speed up the onset of antidepressant action.

Recently the FDA has approved esketamine as a nasal spray for adjunctive therapy in treatment-resistant depression [46]. Esketamine is indicated for depressed patients that did not respond to at least two oral antidepressant monotherapies. It has to be given together with a newly initiated oral antidepressant under strict supervision of certified medical professionals, because of the potential serious adverse effects of esketamine. The launch of a successful potential anti-TRD medication might be a breakthrough in the treatment of depression.

4. Other applications for antidepressants

Apart from treatment of depression, antidepressants and particularly SSRIs and SNRIs are also widely used for treatment of various anxiety disorders, obsessive compulsive disorders, gambling disorders, posttraumatic stress disorder, and various other psychiatric disorders, including alcohol use disorder.

In obsessive compulsive disorder, SSRIs are partially effective, but in general higher doses are needed, and onset of action (6–8 weeks) is slower than in depression. Because comorbidity of depression and anxiety is very high, it appeared that SSRIs could be used as a rational therapy for both disorders, although the disadvantages of SSRIs in depression (side effects, onset of action, partial efficacy) are comparable in anxiety disorder treatment. In Chapter 4, Ballesta and coworkers review and discuss the role of antidepressants in alcohol use disorder (AUD). Because a strong relationship exists between major depression and AUD, the authors investigated the potential role of hippocampal plasticity and neurogenesis in both disorders. By integrating the knowledge of plasticity changes in the hippocampus and its role in both disorders, the authors try to implement shared mechanisms. It is clear that considerable research efforts, both preclinical and clinical, are needed to advance our possibilities to better treat both depression and alcohol use disorder.

5. Conclusion

The emergence of effective antidepressants in the 1960s and 1970s of the last century has led to an explosion of new and often unexpected new discoveries and clinical applications. The development of SSRIs after the serendipitous detection of the first tricyclic antidepressants has revolutionized the treatment of major depression but has also led to new treatments of various anxiety disorders, obsessive compulsive disorder, and various other psychiatric conditions.

Drug treatment always leads to side effects that can be quite cumbersome and often lead to drug discontinuation. Treatment resistance (TRD) is frequently occurring in major depression, and a substantial part of depressed patients (about 30%) does not respond to any treatment. Recent developments (esketamine) promise new approaches in the treatment of TRD although side effects remain a big obstacle.

Research into new and better antidepressants remains urgent but depends primarily on better understanding of the brain mechanisms involved in normal “mood” processing and understanding what is wrong in “depressed” brains. Animal models with high predictive and construct validity are urgently needed to help to discover these (dys)functional mechanisms and deliver new targets for better antidepressants.

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