

challenge has been to define and obtain the right level of functional activity at the D₂ receptor. Aripiprazole is currently the only marketed antipsychotic having this profile, and it has been very successful in treating schizophrenia and a number of other psychiatric diseases. It has recently been introduced as a depot formulation for long-term treatment. Brexpiprazole and cariprazine are in the preregistration phase and display partial D₂ receptor agonism as well as other DA and 5-HT receptor activities, illustrating that DA and 5-HT receptors are still very relevant targets for developing psychiatric drugs.

18.3 TRANSPORTER LIGANDS

18.3.1 ANTIDEPRESSANT DRUGS

Antidepressant drugs represent ligands that target DAT, SERT, and NET to various degrees, and these include first-generation antidepressants (i.e., tricyclic antidepressants [TCAs]), selective serotonin reuptake inhibitors (SSRIs), combined serotonin and NE reuptake inhibitors (SNRIs), and the recently introduced multimodal antidepressants.

The SSRIs have been highly successful in the treatment of depression due to their high safety in use, and a number of additional indications (e.g., panic disorder, obsessive compulsive disorder, and social phobia) have been registered for many of these drugs in addition to major depressive disorder (MDD). However, there are still unmet medical needs in the treatment of depression, such as (1) efficacy in treatment-resistant MDD patients (33% of patients respond inadequately or not at all, even after consecutive treatment with up to four different antidepressants), (2) a rapid onset of antidepressant action (it is generally thought that 2–3 weeks of treatment is needed before a therapeutic response is detected), and (3) effective treatment of residual symptoms (e.g., cognitive symptoms including a diminished ability to think, concentrate, and plan). These unmet needs have driven drug discovery programs in pharmaceutical companies for years and some have been addressed, whereas other unmet needs are still very relevant. In the following, the discovery of the first-generation antidepressants and the SSRIs (exemplified by citalopram and escitalopram) will be discussed. The multimodal antidepressants vilazodone and vortioxetine will be discussed in Section 18.4.

18.3.2 FIRST-GENERATION DRUGS

The pharmacotherapy of depression started in the late 1950s with the introduction of the two drugs iproniazid (**18.17**) and imipramine (**18.19**) (Figure 18.3). Iproniazid was originally an antituberculosis drug, but it was noticed that the drug had an antidepressant effect. It was subsequently discovered that iproniazid was an unselective, irreversible inhibitor of the enzymes MAO-A and MAO-B that deaminate the monoamines NE, DA, and 5-HT. Structural modifications of the tricyclic antipsychotic drugs with chlorpromazine (**18.1**, Figure 18.1) as a prototype led to the 6–7–6 tricyclic compound imipramine (**18.19**) that was found to block the transporters for NE and 5-HT. Both these mechanisms led to an increase in the concentrations of NE and 5-HT in the synapse, which in turn led to the so-called monoamine hypothesis of depression, stating that there is a decreased availability of these neurotransmitters in depression.

Although the discovery of these two classes of drugs was of major therapeutic importance, it quickly turned out that both types had serious fatal side effects. Treatment with MAO inhibitors could induce a hypertensive crisis because of a fatal interaction with foodstuffs containing tyramine such as cheese. Dietary restrictions during treatment with MAO inhibitors were, therefore, required. Reversible MAO-A inhibitors (such as moclobemide [**18.18**]) have later been developed, but such drugs are still not completely devoid of the “cheese effect” because the tyramine potentiation is inherent to blockade of MAO-A in the periphery. MAO inhibitors are, therefore, only used to a lesser extent in antidepressant therapy.