CHAPTER I

Introduction to Antithrombotics and Antipsychotics
1.1 Introduction

1.1.1 Heterocycles

For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. They have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. Heterocycles play an important role in biochemical processes because the side groups of the most typical and essential constituents of living cells, DNA and RNA are based on aromatic heterocycles. Among them approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic, and approximately half are heterocyclic.

In the twentieth century a revolution took place in the design, synthesis and biological activity of the heterocyclic compounds. Among the all drug molecules existing in the market till now heterocyclic compounds occupied 80% in the total volume. It clearly indicates the importance and uses of the heterocyclic compounds due to their potential biological activities than the other drug molecules. The presence of heterocycles in all kinds of organic compounds of interest in biology, pharmacology, optics, electronics, material sciences, and so on is very well known. Between them, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis. The grounds of this interest were their biological activities and unique structures that led to several applications in different areas of pharmaceutical and agrochemical research or, more recently, in material sciences.

The family of sulfur–nitrogen heterocycles includes highly stable aromatic compounds that display physicochemical properties with relevance in the design of new materials, especially those relating to molecular conductors and magnets. During the past few decades, interest has been rapidly growing in gaining insight into the properties and
transformations of these heterocycles. The interesting characteristics found in many of them have led to the development of modern synthetic methods that are the subject of this special issue. Nitrogen and sulfur organic aromatic heterocycles are formally derived from aromatic carbon cycles with a hetero atom taking the place of a ring carbon atom or a complete HC=CH group. The presence of heteroatom results in significant changes in the cyclic molecular structure due to the availability of unshared pairs of electrons and the difference in electro negativity between heteroatom and carbon. Therefore, nitrogen and sulfur heterocyclic compounds display quite different physicochemical characteristics and reactivity from the parent aromatic hydrocarbons. On the other hand, the presence of many nitrogen and sulfur atoms in a ring is normally associated with instability and difficulties in the synthesis but, in fact, stable heterocycles with unusual properties can be frequently obtained from simple organic substrates and the appropriate inorganic reagent. Carbon atoms confer high stability to such rings, according to the aromaticity and antiaromaticity rules, and the nitrogen-sulfur core gives unusual properties to the compounds, in accordance with their electron rich p-excessive nature. The physicochemical properties of these compounds have relevance in the design of new materials, especially concerning organic conductors.

In contrast with the number and variety of such heterocycles, the number of synthetic methods to afford them is, in practice, restricted to the availability of the appropriate sulfur or nitrogen reagent. Sometimes, the preparation of new heterocyclic systems by conventional ways is a tough task that implies many synthetic steps and expensive starting materials. Moreover, many heterocyclic systems, predicted to be stable, are impossible to prepare because the required synthetic approach simply does not exist. For this reason, new approaches to obtain complex heterocyclic systems by using simple organic starting materials and reagents which generate reactive intermediates, that can be trapped by selected nucleophiles in tandem or sequential processes, have been developed. A good combination of reagents and reaction sequences permits the preparation of heterocycles that imply several reaction steps by rational design. As an example, multi
component condensations of carbonyl compounds are powerful synthetic tools for the preparation of structurally diverse complex molecules, which can be further modified by post-condensation transformations. Among the post-condensation transformations, those leading to the formation of heterocyclic cores are very important since they permit the preparation of heterocyclic compounds, often in a very simple manner with substitution patterns that are not easily obtainable by other synthetic routes. Furthermore, these transformations permit a facile access to constrained peptides and peptide mimetic, which are of great interest in drug discovery programs. These and other areas are now currently under intense research, especially those relating to pharmaceutical and new materials chemistry. The interesting characteristics found in many of these heterocycles, the development of rapid synthetic methods from easily available materials, and the very wide range of products obtainable by modern methods offer wide scope for the synthesis of new sulfur-nitrogen heterocycles.

Stereo controlled recognition processes in chemistry, biochemistry and pharmacology have received much attention in modern drug discovery. Due to the asymmetry of bioactive macromolecules including enzymes, G-protein coupled receptors, ion-channels and nucleic acids, the binding of chiral ligands and substrates proceeds stereoselectively. Thus, there is continuous interest in the development of drugs as single enantiomers. The dopamine D_2 and the serotonin 5-HT_2 receptors belong to the G-protein coupled transmembrane receptor family of biomolecules. The dopamine D_2 receptors are expressed in regions associated with motor, limbic and neuroendocrine function, and D_2 antagonists and agonists are used in the treatment of schizophrenia and Parkinson’s disease, respectively. The serotonin 5-HT_2 receptors consist of three subtypes termed 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. They have been implicated in the aetiology of many disease states, and may be particularly important in mental illness, such as depression, anxiety, schizophrenia, migraine and panic disorder. The central dopaminergic and serotonergic pathways are connected anatomically and interact functionally in brain regions implicated in schizophrenia. Many currently used treatments of this disorder act by modulating
dopaminergic and serotonergic tones, although having non-selective effects on postsynaptic receptor subtypes. The development of selective ligands may therefore lead to treatments with increased efficacy and reduced side effects. Additionally, selective ligands may form completely novel therapies.

1.1.2 Active pharmaceutical ingredients

An active pharmaceutical ingredient (API)\textsuperscript{1,2} is the substance in a pharmaceutical drug or a pesticide that is biologically active. Terms in similar use include bulk active in medicine, and active substance in pesticide formulations. Some of the medications and pesticide products may contain more than one active ingredient. The traditional word for the API is pharmacon or pharmakon (from Greek, adapted from pharmacos) which originally denotes a magical substance or drug. A dosage form of a drug is traditionally composed of two things: The API, which is the drug itself; and an excipient also called as bulk pharmaceutical chemical (BPC),\textsuperscript{3} which is the substance of the tablet, or the liquid the API is suspended in or other material that is pharmaceutically inert. Drugs are chosen primarily for their active ingredients. Because homoeopathic products no longer have any biologically active ingredients, their list of ingredients refers to the original ingredients used in their preparation and the finished product no longer contains any active ingredients.

Bulk pharmaceutical chemical containing an active ingredient is encapsulated with other ingredients such as flavors, cooling or heating agents, or sweeteners, within a microsphere. Upon exposure to water or pH, the microsphere releases its contents, and over an extended period of time the BPC release the encapsulated active ingredient via molecular diffusion and enzymatic degradation by lipase. The surface properties of the BPC can be altered to be bioadhesive or negatively or positively charged depending on the intended target site.
1.2 Antithrombotics

Atherothrombosis associated with pre-existing atherosclerotic plaques involves platelet activation, aggregation and thrombus formation. Long-term antiplatelet therapy is effective in the secondary prevention of vascular events in patients with acute coronary or cerebrovascular events that are at a high risk of subsequent thrombotic events. The recent development of drugs with greater selectivity, efficacy and decreased side effects resulted from a better understanding of the mechanisms of atherosclerosis, platelet aggregation, coagulation and thrombolysis.

Endothelial injury caused by shear stress, hypertension, diabetes or smoking is an important factor in the initiation and progression of arterial disease. Lipids and monocytes accumulate on the intima of damaged arteries. Adherent platelets and macrophages secrete growth factors that activate the migration and proliferation of smooth muscle cells from the media. These smooth muscle cells release collagen, proteoglycans and elastic fibers that together form the fibrous cap of the atheromatous plaques. These atheromatous plaques, usually located at vessel Ostia, branches or regions where blood flow changes in velocity or direction, causing high shear stress, later become calcified. High shear stress occurring in the atherosclerotic small arteries and arterioles induces platelet activation, aggregation and enhances platelet thrombus formation.

The disruption of atherosclerotic plaques triggers platelet adhesion, activation and aggregation, causing cerebrovascular, coronary and peripheral vascular ischaemic syndromes that may progress to infarction. Platelet adhesion is mediated by the interaction of platelet glycoprotein Ib/IX with sub endothelial von Willebrand’s factor under high shear conditions, and by platelet glycoprotein Ia/IIb binding to collagen under low shear conditions. The adherent platelets recruit additional platelets into a growing thrombus. Initially, clotting factors assemble on the activated platelet surface and this process enhances thrombin generation. The resultant increase in thrombin activates more platelets and triggers coagulation. The activated platelets also secrete ADP (from their
dense granules), which activates nearby platelets. Thromboxane A\textsubscript{2} released by the platelets activates additional platelets.

### 1.2.1 Thienopyridines

The central role of platelets in the pathophysiology of arterial vascular disease has focused attention on the development of effective platelet inhibitor modalities to mitigate the clinical consequences of atherothrombotic disease.\textsuperscript{7} Aspirin has been the gold standard therapy and is effective in cerebral, coronary and peripheral arterial disease with a 25% reduction in myocardial infarction, stroke and vascular death. The platelet ADP receptor antagonists were developed to further improve the clinical results of therapy.\textsuperscript{8} Thienopyridines are a class of ADP receptor/P2Y\textsubscript{12} inhibitors used for their anti-platelet activity. These are a fascinating family of aromatic compounds with two different heterocyclic rings which still continue to attract the chemical interest. These drugs include: Ticlopidine, Clopidogrel and Prasugrel.\textsuperscript{9}

![Ticlopidine, Clopidogrel, Prasugrel](image)

**Figure 1.1 Thienopyridine derivatives**

Atherosclerosis is a diffuse process that starts early in life, asymptptomatically progressing through adulthood, until clinically manifested.\textsuperscript{10} Atherothrombotic disease is the result of atherosclerosis progression, and its clinical manifestations [acute coronary syndromes (ACS), stroke, etc]. These events are mostly secondary to atherosclerotic plaque disruption and subsequent thrombus formation.\textsuperscript{11,12} Atherosclerosis prevention is mainly focused on the management of the so-called “cardiovascular risk factors” whereas
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Thrombosis-related complications are mainly prevented and/or treated by antithrombotic therapies.

At the site of vascular lesions, platelets adhere to the exposed matrix proteins, prompting platelet activation, resulting in the secretion of multiple platelet agonists mostly modulated by intracellular calcium release. Among them, ADP, thromboxane A₂, thrombin and others play a critical role in maintaining a “pro-platelet-activating” environment. In fact, the understanding of the processes of platelet activation/aggregation and the role of acute thrombus formation on the onset of ACS has led to a widespread use of antiplatelet therapy in cardiovascular disease. Long-term antiplatelet therapy is effective in the secondary prevention of vascular events in patients with acute coronary or cerebrovascular events who are at a high risk of subsequent thrombotic events.

ADP is released from activated platelets, erythrocytes and endothelial cells, and induces platelet adhesion and aggregation. ADP activates platelets by binding to membrane-bound nucleotide receptors (purinoceptors) on the platelet surface called P₂ receptors. Human platelets possess two major G protein-coupled ADP receptors, the P₂Y₁ and P₂Y₁₂ receptors, and a third ionotropic receptor, P₂X₁. The human P₂Y₁ receptor is a Gq protein-coupled receptor that activates phospholipase C to form inositol triphosphate (IP₃) and causes calcium release from intracellular stores. The P₂Y₁ receptor is necessary to trigger a response and initiates the formation of platelet pseudopodia in response to low concentrations of thromboxane A₂ or thrombin, and transient platelet aggregation occurs. However, activation of the P₂Y₁ receptor is insufficient for a full platelet response. The P₂Y₁₂, formerly known as P (2T), P₂T (AC), P₂Y (ADP) or P₂Y (YC), receptor is a Gi protein coupled receptor that inhibits adenylyl cyclase. This results in a decreased platelet cyclic adenosine monophosphate (AMP) level in response to ADP, activating platelet glycoprotein IIb/IIIa (aIIbb3 integrin) receptors that bind fibrinogen, leading to stabilization of platelet aggregation and enhanced platelet secretion. Platelets also possess a third ADP receptor, P₂X₁, which is a ligand gated ion channel that
mediates rapid transient calcium ion influx. However, the P2X₁ receptor does not contribute to platelet aggregation.¹⁴ Aspirin was the first effective platelet inhibitor drug to be identified.

Aspirin results in an irreversible modification of the enzyme cyclo-oxygenase rendering it incapable of converting arachidonic acid into thromboxane A₂. The contribution of aspirin in the reduction of vascular morbidity is significant but is accompanied by several deficiencies, side-effects, while generally not life-threatening but potentially serious. Therefore, the development of new agents has been an appropriate and compelling goal.

Thienopyridines are platelet adenosine diphosphate (ADP) receptor antagonists that were initially developed to provide new opportunities for those patients who are intolerant, resistant, or have failed to respond to other treatments. Clopidogrel (the most widely used thienopyridine) is considered weak and safe anti-platelet agent because it only blocks one of the multiple pathways involved in platelet activation. The thienopyridine derivatives inhibit ADP-induced platelet activation. They produce synergistic effects because they block complementary pathways of platelet aggregation without blocking thrombin-mediated platelet aggregation. In contrast, glycoprotein IIb/IIIa antagonists block aggregation induced by all agonists by preventing cross-linkage of fibrinogen mediated platelet aggregations.

The ADP receptor mediates platelet aggregation primarily through P2Y₁₂ receptors, and to a lesser extent through P2Y₁ receptors.¹⁵ Thienopyridines inhibit ADP receptors through noncompetitive antagonism of the P2Y₁₂ receptor, which in turn inhibits platelet response to other stimuli for platelet aggregation (eg, thromboxane A₂, thrombin). Via transformation of the GPIIb/IIIa receptor, P2Y₁₂ blockade precludes the activated platelet from releasing inflammatory and prothrombotic mediators as well as preventing platelet aggregation.¹⁶ The current agents are Food and Drug Administration (FDA) approved and available include ticlopidine, clopidogrel, and prasugrel.
1.2.1.1 Pharmacology

1.2.1.1.1 Pharmacokinetics of thienopyridines

The chemical structures of clopidogrel and ticlopidine are very similar. Clopidogrel has an additional carboxymethyl side group. Ticlopidine and clopidogrel are inactive in vitro. They are prodrugs and are metabolized in the liver by hepatic cytochrome P450-1A to produce active metabolites that inhibit platelet aggregation by selective and irreversible binding (via covalent bonds) to the P2Y$_{12}$ receptors.\(^\text{17}\) The active metabolite of clopidogrel is a thiol derivative of the parent molecule.\(^\text{16}\) Inhibition of platelet aggregation by these drugs is delayed until 24-48 h after administration, with maximal inhibition achieved after 3-5 days. Recovery of platelet function after drug withdrawal is slow (7-14 days). Clopidogrel, the S-enantiomer of a racemic thienopyridine compound (PCR 4099), is six times more potent than ticlopidine and does not share any common metabolites with ticlopidine.\(^\text{18}\) Between 60 and 70\% of the ADP receptors are sensitive to the effects of the thienopyridines. Maximal inhibition of ADP-induced platelet aggregation after a single oral dose of clopidogrel 375-400 mg is 40–50\% and is achieved in 2-6 h. This level of inhibition is achieved after 3-7 days of repeated dosing with clopidogrel 75 mg administered once a day.\(^\text{19}\) In healthy human volunteer studies, maximal inhibition of platelet aggregation causes a twofold increase in the bleeding time. Platelet function recovers completely 7 days after the discontinuation of clopidogrel therapy in healthy volunteers.

About 50\% of ingested clopidogrel is absorbed rapidly from the gastrointestinal tract and is rapidly hydrolyzed in the liver to the main (85\%) inactive metabolite (a carboxylic acid derivative, SR26334), its bioavailability is unaffected by food or antacids.\(^\text{20}\) The active metabolite has been identified only recently.\(^\text{21}\) Unchanged clopidogrel in the plasma may be detected only 2 h after ingestion. The renal clearance of the principal metabolite (SR26334) is constant over a clopidogrel dose range of 50-150 mg/day, indicating that clopidogrel has linear pharmacokinetics. The elimination half-life of SR26334 is 8 h in young healthy volunteers.\(^\text{20}\) Steady-state pharmacokinetics can be achieved with an
average of 8 days of oral administration.\textsuperscript{22,23} In patients with renal failure, bleeding times are not prolonged with standard doses of clopidogrel, although the renal clearance of the inactive metabolite SR26334 is decreased significantly in patients with severe renal failure. The effect on ADP-mediated platelet aggregation by clopidogrel is not affected by liver disease.\textsuperscript{24} Ticlopidine is rapidly and extensively absorbed from the gastrointestinal tract with an oral bioavailability of 80\%. Ticlopidine is also metabolized by the hepatic cytochrome P450-1A isoenzyme.\textsuperscript{23} The plasma level of the major metabolite peaks 2 h after oral administration.\textsuperscript{25}

1.2.1.2 Synthesis and diagnosis
Synthetic and theoretical interest in the behavior of systems that contain fused $\pi$ rich and $\pi$ deficient ring as well as the search for pharmacologically active substances led to the synthesis of various analogs of quinolines and isoquinolines in which the benzene ring is replaced by thiophene nucleus. Most of the substances described in the literature for thienopyridines systems have been synthesized by traditional methods used to build quinoline and isoquinoline systems.\textsuperscript{26} Recently, a tandem aza–Wittig/electrocyclic ring closure strategy (TAWERS) was used to obtain this nucleus by reacting key imino-phosphorane intermediate with isocyanates or isothiocyanates. Because the interest in preparing novel thiophene analogs of biologically active benzo compounds. Dangi et al.\textsuperscript{27} used a modification in the TAWERS by reacting the imino-phosphorane intermediate with aromatic and heteroaromatic aldehydes to afford biaryl compounds which would display interesting conformational properties. There is so much literature available which describes the synthesis of novel thienopyridines as well as their conformational analysis established by 1D and 2D NMR and X-ray crystallographic studies.\textsuperscript{9}

The Vilsmeier-Haack reaction is a mild but efficient method for the formylation of reactive aromatic substrates. Occasionally, unexpected cyclizations are noted accompanying or following such formylations. This method was applied to the corresponding thiophene giving the thienopyridine (Scheme 1.2).
Scheme 1.1 Reagents and Conditions: (a) EtOOCCH$_2$N$_3$, EtONa, EtOH; (b) PPh$_3$, CH$_2$Cl$_2$; (c) ArCHO.

4. R = Me; Ar = 2’-Fluorophenyl
5. R = H; Ar = 2’, 4’-Difluorophenyl
6. R = Me; Ar = 4’-Quinoline
7. R = Me; Ar = 2’-Quinoline
8. R = H; Ar = (Carbomethoxy-5-thieno[2,3-b]pyrido)
9. R = H; Ar = (2’-Cl, 6’-methoxy-3’-quinoline)
10. R = H; Ar = (2’-Thieno[2,3-b]pyridine)
11. R = H; Ar = 4-(N-benzyl-2’-carbomethoxy-5’-thieno[2,3-b]pyrrolo
12. R = Me; Ar = (2’-Cl, 5’-Br, 3’-pyridine)
13. R = H; Ar = (2’-Cl, 3’-pyridine)

Scheme 1.2 Reagents and Conditions: (a) DMF, POCl$_3$.

(i) Ar = 3-Thienyl
(ii) X = \[
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1.2.1.3 Thienopyridine derivatives discussion

1.2.1.3.1 Ticlopidine
Ticlopidine is a first-generation thienopyridine. It was originally developed in the 1970s and studied as an anti-inflammatory agent. However, its potent antiplatelet effects were more notable.

Mechanism of action
It irreversibly inhibits the ADP receptor, preventing platelet aggregation for the life of the platelet. Despite its efficacy as an ADP receptor antagonist, the wide use of ticlopidine was significantly affected by a rare but severe incidence of neutropenia (8%). For these reasons, clopidogrel, a new agent structurally similar to ticlopidine, but with fewer side-effects (severe neutropenia in 0.5%) emerged as new antiplatelet therapy.

Conclusions
Dual-antiplatelet therapy with ticlopidine is rarely used, as clopidogrel seems to be more effective and better tolerated.

1.2.1.3.2 Clopidogrel
Clopidogrel is a second-generation thienopyridine.

Mechanism of action
Like ticlopidine, it selectively and irreversibly inhibits the P2Y_{12} receptor. Clopidogrel undergoes a process of oxidation by the cytochrome P450 system to generate its active metabolite. There are many datasets demonstrating clopidogrel’s benefits in high-risk patients. Clopidogrel plays an important role in the treatment of heart attacks and is used in the following situations:

- Clopidogrel is used instead of aspirin in patients who have an allergy to aspirin.
- Clopidogrel often is given together with aspirin in treating heart attacks. Studies have shown that the combination of aspirin and clopidogrel is more effective than
aspirin alone in improving survival and limiting damage to heart muscle among patients with heart attacks.

- Clopidogrel is given together with aspirin to patients undergoing PTCA with or without coronary stunting. Studies have shown that the combination of aspirin and clopidogrel is more effective than aspirin alone in preventing formation of blood clots that can re-occlude the coronary artery unblocked by PTCA and in preventing blood clots within recently placed stunts.

- After a heart attack or after PTCA, aspirin is given indefinitely. The optimal duration of clopidogrel has not been established, and duration of use by physicians varies from weeks to months.

- Clopidogrel has almost replaced ticlopidine as a therapeutic antiplatelet agent, used alone or in combination with aspirin. It has proved useful for the prevention of ischemic stroke, myocardial infarction, and vascular death in patients with symptomatic atherosclerosis. Beyond its anti-aggregation effect, it reduces the formation of platelet–leukocyte conjugates in patients with ACS and decreases the expression of activated platelet-dependent inflammatory markers such as CD40 ligand (a potent stimulus of vascular inflammation) and CD62 P-selectin in patients undergoing percutaneous coronary intervention (PCI). In fact, clopidogrel, co-administered with aspirin, is being considered the treatment of choice for prevention of atherothrombotic complications.7

**Resistance and dosing**

Clopidogrel dosing has been a concern, giving significant variability in patient responsiveness. Many patients with hypo responsiveness have been called “clopidogrel resistant”.29,30 First, clinical features, such as diabetes, have been associated with higher pretreatment platelet reactivity, which may not be sufficiently suppressed by recommended doses of clopidogrel. This observation coupled with the fact that insulin alters platelet reactivity might partially explain why diabetics fare worse after ACS.31-33

Second; clopidogrel activation requires the cytochrome P450 enzymatic system, which is
affected by many other drugs. Therefore, there is potential for drug-drug interactions with clopidogrel. Finally, there are certain cellular and genetic factors that appear to underlie a subset of patients who are considered “clopidogrel low responders” or “clopidogrel resistant.” A higher loading dose of 600 mg achieves full antiplatelet effect in 1-2 hours v/s at least 4-6 hours with 300 mg, without a significant increase in major bleeding. A higher loading dose reduced the primary endpoint of death, MI, or TVR within 30 days, driven primarily by a reduction in per procedural MI.

This suggests the possibility of counteracting the increased risk for bleeding during and after surgery in clopidogrel-treated patients by administering platelet units prior to the major surgeries.

Conclusions
Clopidogrel in combination with aspirin has become the standard of care for reducing cardiovascular events in patients with ACS. The ACC/AHA guidelines recommend clopidogrel for 12 months in the setting of DES implantation for ACS, and at least 1 month with BMS implantation.

1.2.1.3.3 Prasugrel
Prasugrel is a novel, third-generation oral thienopyridine. Laboratory results with prasugrel support more potent antiplatelet effects, a lower incidence of interpatient variability in antiplatelet response.

Mechanism of action
It is a specific, irreversible antagonist of the platelet adenosine 5′-diphosphate P2Y_{12} receptor. It is also a prodrug that acts as an irreversible inhibitor of the platelet ADP P2Y_{12} receptor. In contrast with clopidogrel, prasugrel is converted into its active metabolite much more efficiently. Therefore, prasugrel is faster acting and more potent,
with less individual variability. Its rapid absorption and metabolism yields maximal concentrations in a median time of 30 minutes.\textsuperscript{41,42}


derm{Conclusions}
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The greater potency yielded greater efficacy but also more bleeding. First, clopidogrel exhibits substantial inter patient variability. Second, clopidogrel is rather inefficient as a prodrug. Eighty-five percent of its prodrug is hydrolyzed by esterases down a dead-end pathway; therefore, only 15\% is made available to the cytochrome P450 system to convert into an active metabolite. Third, recovery of platelet function is relatively prolonged after clopidogrel administration. Due to these factors, a number of patients on clopidogrel and aspirin continue to experience cardiovascular events.\textsuperscript{7}

\textbf{1.3 Antipsychotics}

Antipsychotics (also known as neuroleptics or major tranquilizers)\textsuperscript{43} are a class of psychiatric medication primarily used to manage psychosis (including delusions, hallucinations, or disordered thought), in particular in schizophrenia and bipolar disorder, and are increasingly being used in the management of non-psychotic disorders (ATC code N05A). The word neuroleptic originated from the Greek word \textit{lepsis} ("seizure" or "fit").
1.3.1 History

Advertisement for Thorazine (chlorpromazine) from the 1950s, reflecting the perceptions of psychosis, including the present discredited perception of a tendency towards violence, from the time of antipsychotics discovery.\textsuperscript{44}

The original antipsychotic drugs were happened upon largely by chance and then tested for their effectiveness. The first, chlorpromazine, was developed as a surgical anesthetic. It was first used on psychiatric patients because of its powerful calming effect; at the time it was regarded as a non-permanent "pharmacological lobotomy".\textsuperscript{45} Lobotomy at the time was used to treat many behavioral disorders, including psychosis, although its effect was to markedly reduce behavioral disorders and mental functioning of all types. However, chlorpromazine proved to reduce the effects of psychosis in a more effective and specific manner than lobotomy, even though it was known to be capable of causing severe sedation. The underlying neurochemistry involved has been studied in detail, and
subsequent antipsychotic drugs have been discovered by an approach that incorporates this sort of information.

The discovery of chlorpromazine's psychoactive effects in 1952 led to huge reduction in the use of restraint, seclusion, and sedation in the management of agitated patients, and also led to further research that resulted in the development of antidepressants, anxiolytics, and the majority of other drugs now used in the management of psychiatric conditions. In 1952, Henri Laborit described chlorpromazine only as inducing indifference towards what was happening around them in nonpsychotic, nonmanic patients, and Jean Delay and Pierre Deniker described it as controlling manic or psychotic agitation. The former claimed to have discovered a treatment for agitation in anyone, and the latter team claimed to have discovered a treatment for psychotic illness.

Until the 1970s there was considerable debate within psychiatry on the most appropriate term to describe the new drugs. In the late 1950s the most widely used term was "neuroleptic", followed by "major tranquilizer" and then "ataractic". The first recorded use of the term tranquilizer dates from the early nineteenth century. In 1953 Frederik F. Yonkman, a chemist at the Swiss based Ciba pharmaceutical company, first used the term tranquilizer to differentiate reserpine from the older sedatives. The word neuroleptic was derived from the Greek: "νεῦρον" (neuron, originally meaning "sinew" but today referring to the nerves) and "λαμβάνω" (lambanō, meaning "take hold of"). Thus, the word means taking hold of one's nerves. This may refer to common side effects such as reduced activity in general, as well as lethargy and impaired motor control. Although these effects are unpleasant and in some cases harmful, they were at one time, along with akathisia, considered a reliable sign that the drug was working. The term "ataraxy" was coined by the neurologist Howard Fabing and the classicist Alister Cameron to describe the observed effect of psychic indifference and detachment in patients treated with chlorpromazine. This term derived from the Greek adjective "ἀτάρακτος" (ataraktos), which means "not disturbed, not excited, without confusion, steady, calm".
the terms "tranquilizer" and "ataractic", medical practitioners distinguished between the "major tranquilizers" or "major ataractics", which referred to drugs used to treat psychoses, and the "minor tranquilizers" or "minor ataractics", which referred to drugs used to treat neuroses. While popular during the 1950s, these terms are rarely used today. They are being abandoned in favor of "antipsychotic", which refers to the drug's desired effects. Today, "minor tranquilizer" refer to anxiolytic and/or hypnotic drugs such as the benzodiazepines and nonbenzodiazepines, which have some antipsychotic properties and are recommended for concurrent use with antipsychotics, and are useful for treating insomnia or drug-induced psychosis. They are powerful (and potentially addictive) sedatives.

Antipsychotics are broadly divided into two groups, the typical or first-generation antipsychotics and the atypical or second-generation antipsychotics. The typical antipsychotics are classified according to their chemical structure while the atypical antipsychotics are classified according to their pharmacological properties. These include serotonin-dopamine antagonists, multi acting receptor targeted antipsychotics (MARTA, those targeting several systems), and dopamine partial agonists, which are often categorized as atypicals.
1.3.2 Typical or First-generation antipsychotics

**Figure 1.2 Butyrophenones**

**Figure 1.3 Diphenylbutylpiperidines**
**Figure 1.4** Phenothiazines
1.3.3 Atypical or Second-generation antipsychotics
Antipsychotics are among the biggest selling and most profitable of all drugs, generating $22 billion in global sales in 2008. By 2003 in the U.S., an estimated 3.21 million patients received antipsychotics, worth an estimated $2.82 billion. Over 2/3 of prescriptions were for the newer more expensive atypicals, each costing on average $164 compared to $40 for the older types. By 2008, sales in the U.S. reached $14.6 billion, the biggest selling drugs in the U.S. by therapeutic class. The number of prescriptions for children and adolescents doubled to 4.4 million between 2003 and 2006, in part because of increases in diagnoses of bipolar disorder.

Figure 1.6 Atypical antipsychotics
Antipsychotics are sometimes administered as part of compulsory psychiatric treatment via inpatient (hospital) commitment or outpatient commitment. They may be administered orally or, in some cases, through long-acting (depot) injections administered in the dorsogluteal, ventrogluteal or deltoid muscle.

First-generation antipsychotics, known as typical antipsychotics, were discovered in the 1950s. Most second-generation drugs, known as atypical antipsychotics, have been developed more recently, although the first atypical antipsychotic, clozapine, was discovered in the 1950s and introduced clinically in the 1970s. Both generations of medication tend to block receptors in the brain's dopamine pathways, but atypicals tend to act on serotonin receptors as well.

Notable and relatively common adverse effects of antipsychotics include extra pyramidal symptoms (which involve motor control) and hyperprolactinaemia primarily in typicals and weight gain and metabolic abnormalities mostly in atypicals.\(^5\)

Antipsychotics are used to treat certain mental disorders according to the indications of a given antipsychotic. In all cases, antipsychotics should only be prescribed after a physician has conducted an initial evaluation and made a plan for appropriate ongoing monitoring.\(^5\) The physician's initial evaluation which precedes a recommendation for using antipsychotics includes physical examination, psychological evaluation, and assessment of any social or environmental concerns.\(^5\) Monitoring includes planning re-evaluation and documentation of dose, efficacy and adverse effects at regular intervals. This is done by conducting tests which would detect movement disorder and neurological symptoms, as well as changes in weight or body mass index, blood pressure, heart rate, blood sugar and lipid profile.\(^5\)

Antipsychotics are prescribed one at a time.\(^5\) In cases in which single antipsychotics are tried alone, and when one of those three cases was Clozapine if possible, then two
Antipsychotics may be prescribed at the same time. In that case, the physician should have a monitoring plan which includes an attempt to deprescribe and only use one antipsychotic.

Antipsychotics are most frequently used for the following conditions:

- **Schizophrenia**
- Schizoaffective disorder most commonly in conjunction with either an antidepressant (in the case of the depressive subtype) or a mood stabilizer (in the case of the bipolar subtype).
- **Bipolar disorder** (acute mania and mixed episodes may be treated with either typical or atypical antipsychotics, although atypical antipsychotics are usually preferred observing how they tend to have more favorable adverse effect profiles and, according to a recent meta-analysis, they tend to have a lower liability for causing conversion from mania to depression. Bipolar depression can be treated with quetiapine, olanzapine or lurasidone. As per bipolar maintenance several atypical antipsychotics have demonstrated efficacy in preventing manic/mixed relapse but few (with the exception of quetiapine and olanzapine have demonstrated efficacy in preventing manic, mixed and depressive relapse as a monotherapy)
- Psychotic depression. In this indication it is a common practice for psychiatrist to prescribe a combination of an atypical antipsychotic and an antidepressant as this practice is best supported by the evidence.
- Treatment-resistant (and not necessarily psychotic) major depression as an adjunct to standard antidepressant therapy.

They are not recommended for dementia or insomnia unless other treatments have not worked. They are not recommended in children unless other treatments are not effective or unless the child has psychosis. Two different antipsychotics should not typically be used for the same person.
Chapter I

1.3.4 Schizophrenia

Treatment guidelines from the British Psychiatric Association\textsuperscript{69} and the American Psychiatric Association recommend antipsychotic drugs as a first line treatment for patients with schizophrenia. The National Institute of Health and Clinical Excellence (NICE) recommends antipsychotic medication in combination with psychosocial therapy, and further recommends that patients expressing a preference for psychosocial therapy alone be informed that better treatment outcomes are achieved in combination with antipsychotic medication.

Placebo-controlled clinical trials have consistently shown superiority for active treatment with an antipsychotic drug compared to treatment with placebo.\textsuperscript{70} The efficacy of such drugs is suboptimal. Few patients achieve complete resolution of symptoms. Response rates, calculated using various cutoff values for symptom reduction, are low and their interpretation is complicated by high placebo response rates and selective publication of clinical trial results.\textsuperscript{71,72} In longer trials, treatment with antipsychotic drugs has shown to be superior to placebo in reducing relapse.\textsuperscript{73}

Some argue that the evidence for antipsychotics from discontinuation-relapse studies may be flawed, because they do not take into account that antipsychotics may sensitize the brain and provoke psychosis if discontinued, which may then be wrongly interpreted as a relapse of the original condition.\textsuperscript{74} Evidence from comparative studies indicates that there may be a subset of individuals with schizophrenia who recover from psychosis without taking antipsychotics, and may do better in the long term than those who take antipsychotics.\textsuperscript{75}

The methods used in trials of antipsychotics, despite stating that the overall quality is "rather good," reported issues with the selection of participants (including that, in schizophrenia trials, in general up to 90\% of people that are suitable do not meet the elaborate inclusion and exclusion criteria, and that negative symptoms have not been
properly assessed despite companies marketing the newer antipsychotics for these); issues with the design of trials (including pharmaceutical company funding of most of them, and inadequate experimental "blinding" so that trial participants could sometimes tell whether they were on placebo or not); and issues with the assessment of outcomes (including the use of a minimal reduction in scores to show "response," lack of assessment of quality of life or recovery, a high rate of discontinuation, selective highlighting of favorable results in the abstracts of publications, and poor reporting of side-effects).  

1.3.5 Bipolar disorder
Antipsychotics are routinely used, often in conjunction with mood stabilizers such as lithium/valproate, as a first-line treatment for manic and mixed episodes associated with bipolar disorder. The reason for this combination is the therapeutic delay of the aforementioned mood stabilizers (for valproate therapeutic effects are usually seen around five days after treatment is commenced whereas lithium usually takes at least a week before the full therapeutic effects are seen) and the comparatively rapid antimanic effects of antipsychotic drugs. The antipsychotics have a documented efficacy when used alone in acute mania/mixed episodes.

Three atypical antipsychotics (lurasidone, olanzapine and quetiapine) have also been found to possess efficacy in the treatment of bipolar depression as a monotherapy. Whereas only olanzapine and quetiapine have been proven to be effective broad-spectrum (i.e. against all three types of relapse-manic, mixed and depressive) prophylactic (or maintenance) treatments in patients with bipolar disorder. A recent Cochrane review also found that olanzapine had a less favorable risk/benefit ratio than lithium as a maintenance treatment for bipolar disorder.

The American Psychiatric Association and the UK National Institute for Health and Clinical Excellence recommend antipsychotics for managing acute psychotic episodes in
schizophrenia or bipolar disorder, and as a longer-term maintenance treatment for reducing the likelihood of further episodes.\textsuperscript{80,83} They state that response to any given antipsychotic can be variable so that trials may be necessary, and that lower doses are to be preferred where possible. A number of studies have looked at levels of "compliance" or "adherence" with antipsychotic regimes and found that discontinuation (stopping taking them) by patients is associated with higher rates of relapse, including hospitalization.

1.3.6 Dementia
Antipsychotics in old age dementia showed a modest benefit compared to placebo in managing aggression or psychosis, but this is combined with a significant increase in serious adverse events. Thus, antipsychotics should not be used routinely to treat dementia with aggression or psychosis, but may be an option in a few cases where there is severe distress or risk of physical harm to others.\textsuperscript{81} Psychosocial interventions may reduce the need for antipsychotics.\textsuperscript{82}

1.3.7 Unipolar depression
A number of second-generation (or \textit{atypical}) antipsychotics have proven to be effective adjuncts in the treatment of major depressive disorder\textsuperscript{83,84} of which aripiprazole, quetiapine, and olanzapine (when used in conjunction with fluoxetine) have received FDA labeling for this indication. Quetiapine has also proven effective as a monotherapy in major depressive disorder.\textsuperscript{85}

1.3.8 Others
Besides the above uses antipsychotics may be used for obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders, tourette syndrome, autism (for which both aripiprazole and risperidone are FDA-labeled) and agitation in those with dementia.\textsuperscript{86} Evidence however does not support the use of atypical antipsychotics in eating disorders or personality disorder.\textsuperscript{87} Risperidone may be useful for obsessive
compulsive disorder.\textsuperscript{86} The use of low doses of antipsychotics for insomnia, while common, is not recommended as there is little evidence of benefit and concerns regarding adverse effects.\textsuperscript{87,88} Low dose antipsychotics may also be used in treatment of impulse-behavioral and cognitive-perceptual symptoms of borderline personality disorder.

In children they may be used in those with disruptive behavior disorders, mood disorders and pervasive developmental disorders or intellectual disability.\textsuperscript{89} Antipsychotics are weakly recommended for Tourette syndrome, there are effective side effects as well.\textsuperscript{90} The situation is similar in autism spectrum disorder.\textsuperscript{91} Much of the evidence for the off-label use of antipsychotics (for example, for dementia, OCD, PTSD, personality disorders, Tourette's) was of insufficient scientific quality to support such use, especially as there was strong evidence of increased risks of stroke, tremors, significant weight gain, sedation, and gastrointestinal problems. A UK review of unlicensed usage in children and adolescents reported a similar mixture of findings and concerns.\textsuperscript{92} A survey of children with pervasive developmental disorder found that 16.5% were taking an antipsychotic drug, most commonly for irritability, aggression, and agitation. Recently, risperidone was approved by the U.S. FDA for the treatment of irritability in children and adolescents with autism.\textsuperscript{93}

Aggressive challenging behavior in adults with intellectual disability is often treated with antipsychotic drugs despite lack of an evidence base. A recent randomized controlled trial, however, found no benefit over placebo and recommended that the use of antipsychotics in this way should no longer be regarded as an acceptable routine treatment.\textsuperscript{94}

\textbf{1.3.9 Typical vs. Atypical}

While the atypical (second-generation) antipsychotics were marketed as offering greater efficacy and reduced side effects than typical medications this may not be true.\textsuperscript{95,96} One review concluded there were no differences\textsuperscript{50} while another\textsuperscript{97} found that atypicals were
"only moderately more efficacious".\textsuperscript{50} These conclusions were, however, questioned by another review, which found that clozapine, amisulpride, olanzapine and risperidone were more effective\textsuperscript{50, 98} Clozapine has appeared to be more effective than other atypical antipsychotics,\textsuperscript{50, 99} although it has been banned previously due to its potentially lethal side effects. While controlled clinical trials of atypicals reported that extra pyramidal symptoms occurred in 5-15\% of patients, a study of bipolar disorder in a real world clinical setting found a rate of 63\%, questioning the generalizability of the trials\textsuperscript{100} Due to bias in the research the accuracy of comparisons of atypical antipsychotics is a concern.\textsuperscript{101}

In 2005, the U.S. government body National Institute of Mental Health published the results of a major independent (not funded by the pharmaceutical companies) multi-site, double-blind study (the CATIE project).\textsuperscript{102} This study compared several atypical antipsychotics to an older typical antipsychotic, perphenazine, among 1493 persons with schizophrenia. The study found that only olanzapine outperformed perphenazine in discontinuation rate (the rate at which people stopped taking it due to its effects). The authors noted an apparent superior efficacy of olanzapine to the other drugs in terms of reduction in psychopathology and rate of hospitalizations, but olanzapine was associated with relatively severe metabolic effects such as a major weight gain problem (averaging 44 pounds (20 kg) over 18 months) and increases in glucose, cholesterol, and triglycerides. The mean and maximal doses used for olanzapine were considerably higher than standard practice, and this has been postulated as a biasing factor that may explain olanzapine's superior efficacy over the other atypical antipsychotics studied, where doses were more in line with clinically relevant practices.\textsuperscript{103} No other atypical antipsychotics (risperidone, quetiapine, and ziprasidone) did better than the typical perphenazine on the measures used, nor did they produce fewer adverse effects than the typical antipsychotic perphenazine, although more patients discontinued perphenazine owing to extra pyramidal effects compared to the atypical agents (8\% vs. 2\% to 4\%).\textsuperscript{56}
Compliance has not been shown to be different between the two types.\textsuperscript{104} 

Many researchers question the first-line prescribing of atypicals over typicals, and some even question the distinction between the two classes.\textsuperscript{105,106,107} In contrast, other researchers point to the significantly higher risk of tardive dyskinesia and extra pyramidal symptoms with the typicals and for this reason alone recommend first-line treatment with the atypicals, notwithstanding a greater propensity for metabolic adverse effects in the latter.\textsuperscript{103,108} The UK government organization NICE recently revised its recommendation favoring atypicals, to advise that the choice should be an individual one based on the particular profiles of the individual drug and on the patient's preferences.

The re-evaluation of the evidence has not necessarily slowed the bias toward prescribing the atypicals.\textsuperscript{109} 

\textbf{1.3.10 Withdrawal symptoms} 
Withdrawal symptoms from antipsychotics may emerge during dosage reduction and discontinuation. Withdrawal symptoms can include nausea, emesis, anorexia, diarrhea, rhinorrhea, diaphoresis, myalgia, paresthesia, anxiety, agitation, restlessness, and insomnia. The psychological withdrawal symptoms can include psychosis, and can be mistaken for a relapse of the underlying disorder. Conversely, the withdrawal syndrome may also be a trigger for relapse. Better management of the withdrawal syndrome may improve the ability of individuals to discontinue antipsychotics.\textsuperscript{110,111} Tardive dyskinesia may abate during withdrawal from the antipsychotic agent, or it may persist.

Withdrawal effects may also occur when switching a person from one antipsychotic to another, (it is presumed due to variations of potency and receptor activity). Such withdrawal effects can include cholinergic rebound, an activation syndrome, and motor syndromes including dyskinesias. These adverse effects are more likely during rapid
changes between antipsychotic agents, so making a gradual change between antipsychotics minimizes these withdrawal effects. The British National Formulary recommends a gradual withdrawal when discontinuing antipsychotic treatment to avoid acute withdrawal syndrome or rapid relapse. The process of cross-titration involves gradually increasing the dose of the new medication while gradually decreasing the dose of the old medication.

1.3.11 Mechanism of action
All antipsychotic drugs tend to block D₂ receptors in the dopamine pathways of the brain. This means that dopamine released in these pathways has less effect. Excess release of dopamine in the mesolimbic pathway has been linked to psychotic experiences. It has also been proven less dopamine released in the prefrontal cortex in the brain, and excess dopamine released from all other pathways, has also been linked to psychotic experiences, caused by abnormal dopaminergic function as a result of patients suffering from schizophrenia or bipolar disorder. Various neuroleptics such as haloperidol and chlorpromazine suppress dopamine chemicals throughout its pathways, in order to normal functioning of dopamine receptors.

In addition of the antagonistic effects of dopamine, antipsychotics (in particular atypical neuroleptics) also antagonize 5-HT₂A receptors. Different alleles of the 5-HT₂A receptor have been associated with schizophrenia and other psychoses, including depression. Higher concentrations of 5-HT₂A receptors in cortical and sub cortical areas, in particular in the right caudate nucleus have been historically recorded. This is the same receptor that psychedelic drugs agonize to various degrees, which explains the correlation between psychedelic drugs and schizophrenia.

Typical antipsychotics are not particularly selective and also block dopamine receptors in the mesocortical pathway, tuberoinfundibular pathway, and the nigrostriatal pathway. Blocking D₂ receptors in these pathways is thought to produce some unwanted side
effects that the typical antipsychotics can produce (see above). They were commonly classified on a spectrum of low potency to high potency, where potency referred to the ability of the drug to bind to dopamine receptors, and not to the effectiveness of the drug. High-potency antipsychotics such as haloperidol, in general, have doses of a few milligrams and cause less sleepiness and calming effects than low-potency antipsychotics such as chlorpromazine and thioridazine, which have dosages of several hundred milligrams. The latter have a greater degree of anticholinergic and antihistaminergic activity, which can counteract dopamine-related side-effects.

Atypical antipsychotic drugs have a similar blocking effect on D₂ receptors, however, most also act on serotonin receptors, especially 5-HT₂A and 5-HT₂C receptors. Both clozapine and quetiapine appear to bind just long enough to elicit antipsychotic effects but not long enough to induce extra pyramidal side effects and prolactin hypersecretion.\textsuperscript{117} 5-HT₂A antagonism increases dopaminergic activity in the nigrostriatal pathway, leading to a lowered extra pyramidal side effect liability among the atypical antipsychotics.\textsuperscript{117,118}

1.3.12 Special populations

Antipsychotics are intended to treat psychotic disorders. However, they are frequently used as a first-line treatment for other conditions in vulnerable populations, and this should not happen.

Antipsychotics should not be used in children or adolescents as a first-line treatment for anything other than a psychotic disorder.\textsuperscript{119} In a concerning trend, in the United States since 2000 the usage of these drugs in young people has greatly increased especially among children from low-income families.\textsuperscript{119} Evidence for the efficacy and tolerability of antipsychotic medications is not sufficient to be able to anticipate all the risks, which include young peoples’ tendency toward weight gain, metabolic side effects, and cardiovascular changes.\textsuperscript{119}
Persons with dementia who exhibit behavioral and psychological symptoms should not be given antipsychotics before trying other treatments.\textsuperscript{120} When taking antipsychotics this population has increased risk of cerebrovascular effects, parkinsonism or extra pyramidal symptoms, sedation, confusion and other cognitive adverse effects, weight gain, and increased mortality.\textsuperscript{120} Physicians and caretakers of persons with dementia should try to address symptoms including agitation, aggression, apathy, anxiety, depression, irritability, and psychosis with alternative treatments whenever antipsychotic use can be replaced or reduced.\textsuperscript{120} Elderly persons often have their dementia treated first with antipsychotics and this is not the best.\textsuperscript{121}

1. 1 Antidepressants

Antidepressants are drugs used for the treatment of major depressive disorder and other conditions, including dysthymia, anxiety disorders, obsessive compulsive disorder, eating disorders, chronic pain, neuropathic pain and in some cases, dysmenorrhea, snoring, migraines, attention deficit hyperactivity disorder (ADHD), substance abuse and sleep disorders. They can be used alone or in combination with other medications.

The most important classes of antidepressants are the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) or atypical antidepressants, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Other drugs used or proposed for the treatment of depression include buprenorphine,\textsuperscript{122} tryptophan,\textsuperscript{123} low-dose antipsychotics,\textsuperscript{124} and St John's wort.\textsuperscript{125}

Selective serotonin reuptake inhibitors (SSRIs)

The SSRIs (selective serotonin reuptake inhibitors) are the most commonly prescribed class of antidepressants. They act on a chemical in the brain called serotonin. The SSRIs include drugs such as fluoxetine, sertraline, and paroxetine.
The SSRIs are preferred over older classes of antidepressants such as tricyclic antidepressants and MAOIs because their adverse effects are less severe.

Figure 1.7 Selective serotonin reuptake inhibitors

Atypical antidepressants or Second-generation antidepressants or Serotonin-norepinephrine reuptake inhibitors (SNRIs)

There are a variety of newer atypical antidepressants which target other neurotransmitters either alone or in addition to serotonin. For example, Bupropion blocks the re-absorption of the neurotransmitters dopamine and norepinephrine. On the other hand, trazodone, duloxetine, venlafaxine, and mirtazapine affect both norepinephrine and serotonin (which is why they are sometimes called serotonin and norepinephrine reuptake inhibitors, or SNRIs).
Tricyclic antidepressants (TCAs)

Tricyclics are among the oldest antidepressants. They work by inhibiting the brain’s reuptake or serotonin and norepinephrine. They also partially inhibit the re-absorption of dopamine. Because the tricyclics have such a broad mechanism of action, they tend to cause more side effects than the other classes of antidepressants. For this reason, the SSRIs and the atypical antidepressants are usually prescribed first.
**Figure 1.9 Tricyclic antidepressants**

*Monoamine oxidase inhibitors (MAOIs)*

MAOIs (monoamine oxidase inhibitors) are the oldest class of antidepressants. MAOIs have severe interactions with certain foods, drinks, and medications. Combining MAO inhibitors with foods or drinks containing tyramine can result in dangerously high blood pressure, which can lead to a stroke or heart attack. Because of this danger, MAOIs are not typically chosen as a first-line depression treatment.

**Figure 1.10 Monoaminoxidase (MAO) inhibitors**
1.4.1 History
Before the 1950s, opioids, amphetamine, and methamphetamine were commonly used as antidepressants. Their use was later restricted due to their addictive nature and side effects.\textsuperscript{126} Extracts from the herb St John's wort had been used as a "nerve tonic" to alleviate depression.\textsuperscript{127}

\textit{Isoniazid, iproniazid, and imipramine}

In 1951, Irving Selikoff and Edward Robitzek, working out of Sea View Hospital on Staten Island, began clinical trials on two new anti-tuberculosis agents developed by Hoffman-LaRoche, isoniazid and iproniazid. Only patients with a poor prognosis were initially treated; nevertheless, their condition improved dramatically. Selikoff and Robitzek noted "a subtle general stimulation, the patients exhibited renewed vigor and indeed this occasionally served to introduce disciplinary problems."\textsuperscript{128} The promise of a cure for tuberculosis in the Sea View Hospital trials was excitedly discussed in the mainstream press.

In 1952, learning of the stimulating side effects of isoniazid, the Cincinnati psychiatrist Max Lurie tried it on his patients. In the following year, he and Harry Salzer reported that isoniazid improved depression in two thirds of their patients and coined the term \textit{antidepressant} to describe its action.\textsuperscript{129} A similar incident took place in Paris, where Jean Delay, head of psychiatry at Sainte-Anne Hospital, heard of this effect from his pulmonology colleagues at Cochin Hospital. In 1952 (before Lurie and Salzer), Delay, with the resident Jean-Francois Buisson, reported the positive effect of isoniazid on depressed patients.\textsuperscript{130} For reasons unrelated to its efficacy, isoniazid as an antidepressant was soon overshadowed by the more toxic iproniazid,\textsuperscript{129} although it remains a mainstay of tuberculosis treatment. The mode of antidepressant action of isoniazid is still unclear. It is speculated that its effect is due to the inhibition of diamine oxidase, coupled with a weak inhibition of monoamine oxidase A.\textsuperscript{131}
Selikoff and Robitzek also experimented with another anti-tuberculosis drug, iproniazid; it showed a greater psycho stimulant effect, but more pronounced toxicity. Later, Jackson Smith, Gordon Kamman, George Crane, and Frank Ayd, described the psychiatric applications of iproniazid. Ernst Zeller found iproniazid to be a potent monoamine oxidase inhibitor. Nevertheless, iproniazid remained relatively obscure until Nathan Kline, the influential and flamboyant head of research at Rockland State Hospital, began to popularize it in the medical and popular press as a "psychic energizer". Roche put a significant marketing effort behind iproniazid, including promoting its off-label use for depression. Its sales grew until it was recalled in 1961, due to reports of lethal hepatotoxicity.

The antidepressant effect of a tricyclic, a three ringed compound, was first discovered in 1957 by Roland Kuhn in a Swiss psychiatric hospital. Antihistamine derivatives were used to treat surgical shock and later as neuroleptics. Although in 1955 reserpine was shown to be more effective than placebo in alleviating anxious depression, neuroleptics were being developed as sedatives and antipsychotics.

Attempting to improve the effectiveness of chlorpromazine, Kuhn-in conjunction with the Geigy Pharmaceutical Company discovered the compound "G 22355", later renamed imipramine. Imipramine had a beneficial effect in patients with depression who showed mental and motor retardation. Kuhn described his new compound as a "thymoleptic" "taking hold of the emotions," in contrast with neuroleptics, "taking hold of the nerves" in 1955-56. These gradually became established, resulting in the patent and manufacture in the U.S. in 1951 by Häfliger and Schinder.

1.4.1.1 Second generation antidepressants
Antidepressants became prescription drugs in the 1950s. It was estimated that no more than 50 to 100 individuals per million suffered from the kind of depression that these new drugs would treat, and pharmaceutical companies were not enthusiastic in marketing for
this small market. Sales through the 1960s remained poor compared to the sales of tranquilizers, which were being marketed for different uses.\textsuperscript{135} Imipramine remained in common use and numerous successors were introduced. The use of monoamine oxidase inhibitors (MAOI) increased after the development and introduction of "reversible" forms affecting only the MAO-A subtype of inhibitors, making this drug safer to use.\textsuperscript{135,136}

By the 1960s, it was thought that the mode of action of tricyclics was to inhibit norepinephrine reuptake. However, norepinephrine reuptake became associated with stimulating effects. Later tricyclics were thought to affect serotonin as proposed in 1969 by Carlsson and Lindqvist as well as Lapin and Oxenkrug.

Researchers began a process of rational drug design to isolate antihistamine-derived compounds that would selectively target these systems. The first such compound to be patented was zimelidine in 1971, while the first released clinically was indalpine. Fluoxetine was approved for commercial use by the U.S. Food and Drug Administration (FDA) in 1988, becoming the first blockbuster SSRI. Fluoxetine was developed at Eli Lilly and Company in the early 1970s by Bryan Molloy, Klaus Schmiegel, David Wong and others.\textsuperscript{137,138} SSRIs became known as "novel antidepressants" along with other newer drugs such as SNRIs and NRIs with various selective effects.\textsuperscript{139}

St John's wort fell out of favor in most countries through the 19\textsuperscript{th} and 20\textsuperscript{th} centuries, except in Germany, where Hypericum extracts were eventually licensed, packaged and prescribed. Small-scale efficacy trials were carried out in the 1970s and 1980s, and attention grew in the 1990s following a meta-analysis.\textsuperscript{140} It remains an over-the-counter drug (OTC) supplement in most countries. Research continues to investigate its active component hyperforin, and to further understand its mode of action.\textsuperscript{141,142}

In the United Kingdom, the use of antidepressants increased by 234\% in the 10 years up to 2002. In the U.S. a 2005 independent report stated that 11\% of women and 5\% of men
in the non-institutionalized population (2002) take antidepressants. A 1998 survey found that 67% of patients diagnosed with depression were prescribed an antidepressant. A 2007 study suggested that 25% of Americans were over diagnosed with depression, regardless of any medical intervention. The findings were based on a national survey of 8,098 people.

A 2002 survey found that about 3.5% of all people in France were being prescribed antidepressants, compared to 1.7% in 1992, often for conditions other than depression and often not in line with authorizations or guidelines. Between 1996 and 2004 in British Columbia, antidepressant use increased from 3.4% to 7.2% of the population. Data from 1992 to 2001 from the Netherlands indicated an increasing rate of prescriptions of SSRIs, and an increasing duration of treatment. Surveys indicate that antidepressant use, particularly of SSRIs, has increased rapidly in most developed countries, driven by an increased awareness of depression together with the availability and commercial promotion of new antidepressants. Antidepressants are also increasingly used worldwide for non-depressive patients as studies continue to show the potential of immunomodulatory, analgesic and anti-inflammatory properties in antidepressants.

The choice of a particular antidepressant is reported to be based, in the absence of research evidence of differences in efficacy, on seeking to avoid certain side-effects, and taking into account comorbid (co-occurring) psychiatric disorders, specific clinical symptoms and prior treatment history.

It is also reported that, despite equivocal evidence of a significant difference in efficacy between older and newer antidepressants, clinicians perceive the newer drugs, including SSRIs and SNRIs, to be more effective than the older drugs (tricyclics and MAOIs). Currently, the most commonly prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs), even though a Cochrane systematic review found no major difference
in efficacy between SSRIs and tricyclic antidepressants.\textsuperscript{150} A survey in the UK found that male general physicians were more likely to prescribe antidepressants than female doctors.

The number of antidepressants prescribed by the National Health Service (NHS) in the UK almost doubled during one decade, authorities reported in 2010. Furthermore the number increased sharply in 2009 when 39.1 million prescriptions were issued, compared to 20.1 million issued in 1999. Also, physicians issued 3.18 million more prescriptions in 2009 than in 2008. Health authorities believed the increase was partly linked to the recession. However, other reasons include a diagnosis improvement, a reduction of the stigma on mental ill-health, and more distress caused by the economic crisis. Furthermore, physicians' concern is that some people who exhibit milder symptoms of depression are being prescribed drugs unnecessarily due to the lack of other options including talk therapies, counseling and cognitive behavioral therapy. One more factor that may be increasing the consumption of antidepressants is that, these medications now are used for other conditions including social anxiety and post traumatic stress.\textsuperscript{151}

The use of antidepressants in the U.S. doubled over one decade, from 1996 to 2005. Antidepressant drugs were prescribed to 13 million in 1996 and to 27 million people by 2005. In 2008, more than 164 million prescriptions were written. During this period, patients were less likely to undergo psychotherapy.

1.4.2 Mild depression
Various researchers have contested the ability of antidepressants to relieve depression, skeptical that the drugs aid patients significantly more than placebo. A review of antidepressant trials submitted to the FDA by the industry for drug approval revealed that when a trial was successful, the results of the trial was published 94\% of the time, however, when the trial was not found to be more effective than placebo, it was only published 50\% of the time. This demonstrated a measure of bias in reporting by industry.
Combined, 51% of all studies showed efficacy. The difference in effect between active placebos and several antidepressants appeared small and strongly affected by publication bias.

Controversy regarding the efficacy of antidepressants has arisen due to studies showing that antidepressants fail to provide significantly greater efficacy than placebo in some studies. A 2002 study claimed that the difference between antidepressants and placebo is close to negligible. A meta-analysis done by two psychologists led them to believe that although the drugs did help people, the difference between the pills and placebo was not meaningful for patients; a later publication by the same author concluded newer-generation medicines were below the criteria of clinical significance. Another study focusing on paroxetine (Paxil) and imipramine found that antidepressant drugs were hardly better than placebo in cases of mild or moderate depression they surveyed.

A study published in the *Journal of the American Medical Association (JAMA)* demonstrated that the magnitude of the placebo effect in clinical trials of depression have been growing over time, while the effect size of tested drugs has remained relatively constant. The authors suggest that one possible explanation for the growing placebo effect in clinical trials is the inclusion of larger number of participants with shorter term, mild, or spontaneously remitting depression as a result of decreasing stigma associated with antidepressant use.

The Cochrane Collaboration recently performed a systematic review of clinical trials of the generic antidepressant amitriptyline. The study concluded that in spite of moderate evidence for publication bias, there is strong evidence that the efficacy of amitriptyline is superior to placebo. A review commissioned by the National Institute for Clinical Excellence concluded that there is strong evidence that SSRIs have greater efficacy than placebo on achieving a 50% reduction in depression scores in moderate and severe major depression, and that
there is some evidence for a similar effect in mild depression. The treatment guidelines developed in conjunction with this review suggest that antidepressants should be considered in patients with moderate to severe depression and those with mild depression that is persistent or resistant to other treatment modalities.

In 2005, antidepressants became the most prescribed drug in the United States, causing more debate over the issue. Some doctors believe this is a positive sign that people are finally seeking help for their issues. Others disagree, saying that this shows that people are becoming too dependent on antidepressants.

In 2012, Aimee Hunter and her team used electroencephalography (EEG) and showed that taking placebo decreased pre-frontal brain activity in those subjects who had prior use of antidepressants, similar to the expected antidepressant response, but increased brain activity in antidepressant-naive subjects. She attributed this antidepressant response of placebo, in repeat users, to a memory effect.

However, the later experiment conducted by John H. Krystal at Yale University School of Medicine to assess whether growth mixture modeling can provide insights into antidepressant and placebo responses in clinical trials of patients with major depression showed that duloxetine and SSRI did not differ in efficacy, and compared with placebo they significantly decreased the odds of following the nonresponder trajectory. Antidepressant responders had significantly better Hamilton Depression Rating Scale (HAM-D) scores over time than placebo-treated patients, but antidepressant nonresponders had significantly worse HAM-D scores over time than the placebo-treated patients.158
1.4.3 Withdrawal symptoms
If an SSRI is suddenly discontinued, it frequently produces an event of "SSRI discontinuation syndrome" that has a both a bodily and psychological withdrawal component.\textsuperscript{159}

Withdrawal syndromes have been reported with TCAs,\textsuperscript{160} MOAIs,\textsuperscript{161} SNRIs,\textsuperscript{162} and SSRIs. Researchers from the Nordic Cochrane Center in Denmark compared the signs and symptoms of SSRI discontinuation to those of the benzodiazepine withdrawal syndrome\textsuperscript{163} and concluded that the withdrawal reactions were so similar that both withdrawal reactions indicated a dependence syndrome. Elsewhere, concerns have been raised that SSRIs cause dependence.\textsuperscript{164}

When treatment is prolonged over 6-9 months, processes oppose the initial effects of antidepressant drugs (loss of clinical effects). When drug treatment ends, these processes may be unopposed and yield withdrawal symptoms and increased vulnerability to relapse. Such processes are not necessarily reversible. The more antidepressants are switched or potentiated, the more likely oppositional tolerance can take place.\textsuperscript{165}

Some of the withdrawal symptoms of SSRI discontinuation include: nausea, chills, muscles aches, dizziness, anxiety, irritability, insomnia, fatigue, and in some patients, electric shock sensations.\textsuperscript{166,167} Moreover, when changes in antidepressant dosage occur, whether up or down, a doubling of the risk of suicide is seen.\textsuperscript{168}

To minimize the intensity of withdrawal and rebound effects\textsuperscript{169} antidepressants should be discontinued over a period of several weeks or months depending on a person's response to reductions. A suggested regimen is a decrease in the SSRI by about 25% per week. This is a guideline; the actual amount of time required to withdraw from a given antidepressant is unique to the drug. Certain antidepressants may have long half-lives and remain in the person's system for a period of time long enough to prevent a sudden "drop"
in concentration, meaning that withdrawal or rebound effects are unlikely or less pronounced.

Most cases of discontinuation syndrome last between one and four weeks but a substantial minority, perhaps up to 15% of users, have persistent withdrawal symptoms evident one year post-withdrawal.\textsuperscript{170} Paroxetine and venlafaxine\textsuperscript{161,166,171-175} seem to be particularly difficult to discontinue and prolonged withdrawal syndrome lasting over 18 months have been reported with paroxetine.\textsuperscript{172} Peer-support groups exist to help patients taper off of their antidepressants.

1.4.4 Pharmacology

The earliest and probably most widely accepted scientific theory of antidepressant action is the monoamine hypothesis (which can be traced back to the 1950s), which states that depression is due to an imbalance (most often a deficiency) of the monoamine neurotransmitters (namely serotonin, norepinephrine and dopamine).\textsuperscript{176} It was originally proposed based on the observation that certain hydrazine anti-tuberculosis agents produce antidepressant effects, which were later linked to their inhibitory effects on monoamine oxidase, the enzyme that catalyses the breakdown of the monoamine neurotransmitters.\textsuperscript{176} All currently marketed antidepressants have the monoamine hypothesis as their theoretical basis, with the possible exception of agomelatine which acts on a dual melatonergic-serotonergic pathway.\textsuperscript{176} Despite the success of the monoamine hypothesis it has a number of limitations: for one, all monoaminergic antidepressants have a delayed onset of action of at least a week; and secondly, there are a sizeable portion (>40%) of depressed patients that do not adequately respond to monoaminergic antidepressants.\textsuperscript{177,178} Further evidence to the contrary of the monoamine hypothesis are the recent findings that a single intravenous infusion with ketamine, an antagonist of the NMDA receptor-a type of glutamate receptor-produces rapid (within 2 hours), robust and sustained (lasting for up to a fortnight) antidepressant effects.\textsuperscript{178} To overcome these flaws with the monoamine hypothesis a number of alternative hypotheses have been proposed,
including the glutamate, neurogenic, epigenetic, cortisol hyper secretion and inflammatory hypotheses.\textsuperscript{177-180}
1.5 References and notes


27. Dangi, G.; Bele, D. S.; Sharma, K. *Journal of Drug Delivery & Therapeutics* 2011, 1, 8.


44. The text reads: "When the patient lashes out against 'them' - THORAZINE (brand of chlorpromazine) quickly puts an end to his violent outburst. 'Thorazine' is especially effective when the psychotic episode is triggered by delusions or hallucinations. At the outset of treatment, Thorazine's combination of antipsychotic and sedative effects provides both emotional and physical calming. Assaultive or destructive behavior is rapidly controlled. As therapy continues, the initial sedative effect gradually disappears. But the antipsychotic effect continues, helping to dispel or modify delusions, hallucinations and confusion, while keeping the patient calm and approachable. Smith Kline and French Laboratories leaders in psycho pharmaceutical research."


114. Stahl, S. M. *Stahl's Essential Psychopharmacology: Neuroscientific basis and practical applications* Cambridge University Press, **2008**.


119. American Psychiatric Association, "Five Things Physicians and Patients
Should Question", Choosing Wisely: an initiative of the ABIM Foundation 2013, which cites


(iv) Zito, J. M.; Burcu, M.; Ibe, A.; Safer, D. J.; Magder, L. S. Psychiatric Serv. 2013, 64, 223.

American Psychiatric Association, "Five Things Physicians and Patients Should Question", Choosing Wisely: an initiative of the ABIM Foundation 2013, which cites


American Geriatrics Society, "Ten Things Physicians and Patients Should Question", Choosing Wisely: an initiative of the ABIM Foundation 2013, which cites


Chapter I


