

History of the Use of Antidepressants in Primary Care

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As the “gatekeepers” of medical care in the United States, primary care physicians are likely to be the first to detect and treat individuals experiencing psychiatric illnesses. The author provides a brief historical overview of the emergence of psychopharmacology, the development and use of antidepressant drugs, and an examination of their expanding use in primary care for the treatment of both psychiatric disorders, such as mood and anxiety disorders, and general medical conditions, such as chronic pain disorders. *(Primary Care Companion J Clin Psychiatry 2003;5[suppl 7]:6–10)*

Although psychoactive drugs (i.e., substances that directly participate in the ongoing function of the nervous system) have been used for medical, cultural, religious, and recreational purposes for thousands of years, it is only during the last 100 years that the view of psychoactive drugs as magical potions and recreational agents has begun to be tempered by the rise of science, advances in chemistry, and changes in cultural traditions and mores. Within this larger historical context, psychopharmacology emerged relatively recently as an established science, yielding important classes of therapeutic agents targeting psychosis, depression, and anxiety. The effectiveness, safety, and tolerability of many of these agents have rendered them among the most widely used prescription agents in the world.

ORIGIN OF MODERN PSYCHOPHARMACOLOGY

The roots of psychopharmacology as a scientific discipline can be traced to the late 19th century when drug treatments such as lithium were used for inmates of insane asylums, though the mechanisms of both the illnesses and the drugs being used to treat them remained poorly understood. In the early 20th century, experimental testing of the scientific basis of psychoactive effects of drugs with opioid alkaloids led to coining of the term *psychopharmacology*.¹ This period also witnessed many attempts to treat depressed patients by using psychoactive substances. As only marginal success was seen with stimulants and

chemical shock treatments, electroconvulsive therapy remained the treatment of choice for depressed patients throughout the first half of the 20th century. It was not until the 1950s that major breakthroughs in psychopharmacology occurred (Figure 1).

The molecular manipulation of antihistamines led to the first important breakthrough: synthesis of phenothiazines by Charpentier at Rhone-Poulenc and the development of chlorpromazine as an antipsychotic agent.² Chlorpromazine was found to exert potent tranquilizing effects and relieve symptoms such as aggression and hallucinations. Researchers in molecular chemistry took great interest in the development of chlorpromazine and began to systematically alter the structure of antihistamines and other psychoactive agents in the search for potential therapies. Despite these systematic efforts, serendipity played a large role in the discovery of the first modern antidepressant agents.

DISCOVERY OF ANTIDEPRESSANTS

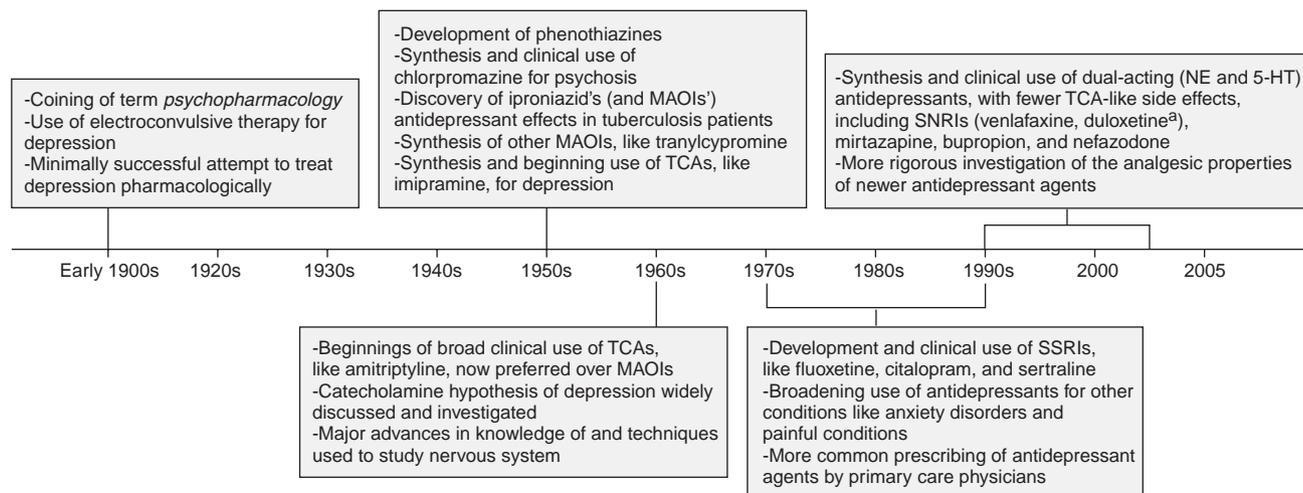
In 1952, while being studied as a possible treatment for tuberculosis, the antimycobacterial agent iproniazid was discovered to have psychoactive properties. It was noted that even terminally ill patients who were given this drug became cheerful, more optimistic, and more physically active.³ Soon after its development, Zeller⁴ showed that iproniazid and its cousins slowed the enzymatic breakdown of the monoamines norepinephrine (NE), serotonin (5-HT), and dopamine (DA) via inhibition of the mitochondrial enzyme monoamine oxidase—hence this class became known as monoamine oxidase inhibitors (MAOIs). Despite this reported effect, MAOIs were not used clinically for treatment of depressed patients until almost a decade later.⁵ Development of distinctly different antidepressant agents, separate from the MAOIs, also occurred during this time. Molecular modifications of phenothiazines led to synthesis of imipramine, the first clinically useful tricyclic antidepressant (TCA).⁶ These agents were found to block the removal or “reuptake” of NE and 5-HT from the synapse,

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Figure 1. A Brief Overview of the Development of Psychopharmacology and Antidepressants During the 1900s and 2000s



^aInvestigational compound in clinical development.

Abbreviations: MAOI = monoamine oxidase inhibitor, NE = norepinephrine, 5-HT = serotonin, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

thus increasing the levels of these transmitters available for binding with receptors. While MAOIs and TCAs presented major advances in treatment of depressed patients, their use was hindered by significant safety and toxicity issues, unpleasant side effects like sedation, as well as potentially dangerous drug and substance interactions. Further modifications of the phenothiazine molecule yielded comparatively safer and better-tolerated TCAs, including desipramine and amitriptyline.

Coincident with the advances made throughout the 1960s and 1970s in synthesizing and identifying psychoactive drugs useful in the treatment of a variety of mental illnesses, great strides were being made in our understanding of the basic functional elements of the nervous system as well as the tools available to study them (Figure 1). For instance, scientists now understood that psychoactive drugs usually interact with receptors located on neurons and that such interaction changes neural functioning. Technical advances like ultracentrifugation, functional imaging techniques, and the ability to trace and measure radioactively labeled substances also aided investigation of brain function. With these leaps in basic neuroscientific knowledge and growing clinical experience with psychoactive drugs, clinicians and researchers were better equipped to formulate working hypotheses about the causes of specific mental illnesses and to elucidate the mechanisms by which psychoactive drugs exerted their behavioral effects.

The catecholamine hypothesis of emotion and its relation to depression was of wide interest^{7,8} and held that decreased levels of certain neurotransmitters, such as NE, DA, and 5-HT, might play a role in the pathogenesis of depression. Later refinements of this original proposal led

to the notion that depression was primarily due to NE deficits,^{8,9} based in part on the fact that agents that relieve depression increase brain NE levels. However, others claimed that decreased brain levels of 5-HT play an important role in the pathogenesis of depression (e.g., “the serotonin hypothesis”).¹⁰ Fueled by the serotonin hypothesis of depression, a search for structural analogs of diphenhydramine (shown to be inactive against NE but active against 5-HT) with antidepressant properties led to the development of fluoxetine, the first selective serotonin reuptake inhibitor (SSRI).¹¹

USE OF ANTIDEPRESSANTS IN PRIMARY CARE

Depression

The improved safety and tolerability profile of the SSRIs and relatively comparable efficacy in depressed outpatients, compared with that of TCAs and MAOIs, represented yet another important advance in the treatment of depression (Figure 1). In sharp contrast to the 1950s through the 1970s, when most patients with depression were treated by a psychiatrist, the effectiveness, ease of use, and good patient tolerability with SSRIs made treatment in primary care the norm rather than the exception. Today, primary care physicians are among the most frequent prescribers of newer-generation antidepressant medications in the United States, and some depressed patients never receive treatment from a psychiatrist.

An Emerging Unmet Need

In comparison with patients seen in a psychiatric setting, patients with depression are most likely to present

to their primary care physician with somatic complaints, such as vague, nonspecific pain (e.g., headaches, muscle aches), feelings of malaise, decreased energy, insomnia, and headaches. Patients often do not volunteer information about their emotional well-being.¹² Perhaps due to patient reluctance to discuss emotional difficulties and other variables, such as the broad variation of symptoms presented and limited time for interaction with patients, recognition of major depressive disorder by primary care clinicians remains a challenge.¹² A study showing that primary care physicians missed the diagnosis of major depressive disorder in 66% of patients with the illness¹³ demonstrates that there are opportunities to improve screening and diagnosis in the primary care setting. Moreover, primary care physicians must overcome challenges such as limited opportunities to provide psychosocial support at patient visits, the delayed and variable response to different types of antidepressant agents, and the potential complication of psychic and somatic symptoms from comorbid conditions.

Other Conditions

The increasing and evolving use of antidepressants over the last 40 years has also brought about significant changes in treatment of other conditions often comorbid with depression. Astute clinicians quickly observed that MAOIs and TCAs were effective for treatment of anxiety and the relief of chronic pain conditions.^{6,14,15} Similarly, SSRIs and newer classes of antidepressants were found to be effective in the management of anxiety and, to a lesser degree, chronic pain relief.¹⁶⁻¹⁸

The use of TCAs in a variety of chronic painful conditions, such as diabetic neuropathy and postherpetic neuralgia, is based on a well-established antinociceptive effect that is independent of any antidepressant actions.¹⁹⁻²⁴ Analgesia with TCAs is seen at lower doses than those typically required for antidepressant effects, and the onset of analgesic action occurs comparatively sooner.²⁰ Researchers attribute the analgesic effects of TCAs and other antidepressants to augmentation of signaling from the descending cortical, supraspinal, and spinal pathways that release 5-HT and NE to inhibit, via a number of mechanisms, pain transmission from the periphery to the central nervous system.²⁵

Recent meta-analyses of animal and human experimental trials indicate that antidepressants that increase central levels of both NE and 5-HT, such as dual-acting TCAs like amitriptyline, are more effective in relieving pain than agents with more selective actions on NE or 5-HT (e.g., nortriptyline, maprotiline, or SSRIs like fluoxetine and sertraline).²⁶ A number of clinical trials indicate that up to three quarters of patients with chronic pain, as with migraine or tension headache, poststroke pain, and diabetic or postherpetic neuralgia, experience significant pain relief when treated with amitriptyline.^{20,21,27-29} By con-

trast, antidepressants that selectively inhibit reuptake of either 5-HT or NE have yielded mixed analgesic success in patients with chronic painful conditions. Among randomized controlled clinical trials, significant relief has been demonstrated by some,^{16,17,30,31} while others have failed to demonstrate analgesic effects exceeding those observed with placebo or demonstrated analgesia of lesser magnitude than that seen with amitriptyline or imipramine.^{20,21,32-34}

It has been suggested that such mixed results may be related to variation among patients or between disease pathologies with respect to the relative contributions of serotonergic and noradrenergic modulation of nociception.²¹ Observations from some studies of SSRIs like fluoxetine further indicate that clinical improvements in pain may be partially accounted for by these agents' antidepressant effects.^{20,31} These data suggest that selective antidepressant NE or 5-HT modulators may be less reliably effective than dual-acting antidepressants like amitriptyline.³⁵ However, as with treatment of depression, use of TCAs for chronic pain is limited by significant side effects related to nonspecific binding at histaminergic and cholinergic receptors, giving rise to sedation, cognitive impairments, postural hypotension, tachycardia, constipation, and dry mouth.

Recent Developments

In recent years, a number of antidepressants with dual NE and 5-HT action like those seen with the tertiary amine TCAs, but with minimal or no nonselective histaminergic or cholinergic effects, have been developed. These compounds include the serotonin-norepinephrine reuptake inhibitors (SNRIs) venlafaxine and duloxetine and the noradrenergic and specific serotonergic antidepressant mirtazapine.

Around the same time, developments in research led to new recommendations for the goal of antidepressant treatment. Clinical guidelines suggested that, although a response to treatment represents a significant improvement for depressed patients, clinicians should strive to treat their patients to remission, which is characterized by virtually no symptoms of depression and a return to normal functioning for the patient.³⁶⁻³⁹ Remission continues to be recognized as the optimal treatment outcome for depression.

Dual-acting antidepressants presented primary care clinicians with additional treatment options that, like SSRIs, were effective, safe, and easy to prescribe for their depressed patients. A broad selection of treatment options with differing mechanisms was an important development as the focus on efficacy shifted from response to remission. While it has been well established that available antidepressants are all effective treatment options, evidence of differences in efficacy between dual-acting agents and SSRIs has emerged. Meta-analyses have reported that, although the SSRIs may have a tolerability advantage, dual-acting TCAs seem to be more effective than SSRIs for treating inpatients and patients with severe depression.⁴⁰

More recently, results of pooled analyses have demonstrated that treatment with the SNRI venlafaxine is more likely to bring patients to remission compared with SSRIs.^{41,42}

With respect to analgesia, venlafaxine is the most extensively studied of the newer agents. Evidence from animal investigations suggests that the antinociceptive effects of venlafaxine, as seen with TCAs,⁴³⁻⁴⁵ may involve not only 5-HT and NE mechanisms but also indirect modulation of kappa and sigma opioid receptors.⁴⁶ Similar modulation of opioid systems has been suggested with TCAs and nefazodone as well.⁴⁷ In addition to case reports citing successful treatment of patients with venlafaxine for various types of painful conditions refractory to other analgesic treatments,⁴⁸⁻⁵⁰ a number of clinical trials and investigations in healthy volunteers indicate that it effectively relieves neuropathic pain and increases the pain threshold.⁵¹⁻⁵⁴ Data on the analgesic effects of the other agents in this category are more limited, although preliminary evidence with duloxetine and mirtazapine is encouraging.^{55,56}

FUTURE AREAS OF RESEARCH

The underlying pathologic mechanisms linking depressive dysphoria, insomnia, and somatic complaints remain poorly understood. The inadequacy of the catecholamine hypothesis of depression in explaining such phenomena has long been recognized and the mechanism by which antidepressant agents exert their therapeutic effects is still quite unclear. Future research must work toward revealing the critical events that give rise to depression; as knowledge of the causes of depression grows, our ability to treat it successfully will also be enhanced.

The nature of the neurophysiologic and neuroanatomic substrates that account for the frequent comorbidity of chronic pain and depression also has not been clearly delineated. Throughout the emergence of psychopharmacology as a scientific discipline, there are many striking examples demonstrating that substances found to be useful in treating a given disorder often lead to a better understanding of the underlying disease processes. Such logic led to the formulation of the catecholamine hypothesis, which has guided research in the treatment of depression for the last 4 decades. In keeping with this principle, a clear understanding of the pharmacologic actions of antidepressant agents continues to hold the promise of helping us to understand the common threads that link together depression and pain.

SUMMARY

Since its inception during the early 20th century, psychopharmacology has wrought important and far-reaching medical and social changes. Among the most important of these has been the discovery of antidepressant

agents. Identification of the MAOI iproniazid and, later, the TCAs imipramine and amitriptyline ushered in a new era of psychiatric medicine. With advances continuing in the 1970s and 1980s, development of the safer and better tolerated SSRIs shifted antidepressants and, subsequently, the treatment of the majority of depressed patients into the hands of primary care physicians. Finally, a third, post-SSRI generation of antidepressants became available, including agents such as mirtazapine and the SNRI venlafaxine; these agents have in common the property of exerting combined effects on NE and 5-HT, while largely lacking the nonspecific and problematic actions at histaminergic and cholinergic receptors seen with TCAs. The utility of antidepressants quickly expanded to include other conditions: many antidepressants also effectively treat anxiety disorders and the chronic pain associated with disorders such as diabetic and postherpetic neuralgia.

Analgesia with antidepressant treatment appears to be mediated by both noradrenergic and serotonergic signaling, as well as opioid mechanisms. An extensive body of evidence shows that TCAs, particularly those that modulate both NE and 5-HT signaling, reliably relieve pain, while analgesia with SSRI treatment is of lesser magnitude or is less reliably produced. A growing body of evidence indicates that the newer and more selective dual-acting antidepressants like venlafaxine and mirtazapine also possess analgesic properties. The development and continued investigation of the analgesic effects of these newer antidepressant agents is likely not only to enhance treatment of depression and chronic painful conditions, but also to help elucidate the pathophysiologic processes underlying these disorders.

Drug names: amitriptyline (Elavil, Limbitrol, and others), chlorpromazine (Thorazine, Sonazine, and others), desipramine (Norpramin and others), diphenhydramine (Benadryl and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), lithium (Eskalith, Lithobid, and others), maprotiline (Ludiomil and others), mirtazapine (Remeron and others), nefazodone (Serzone), nortriptyline (Aventyl, Pamelor, and others), sertraline (Zoloft), venlafaxine (Effexor).

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