Serendipity and Psychopharmacology

ABSTRACT
This article describes several examples where the development of drugs and devices for use in psychiatry followed from initial serendipitous observations. The potential psychotropic properties of chlorpromazine (Thorazine®) were first noted in surgical patients when the drug was being investigated as a potentiator of anesthesia. Similar findings were noted with iproniazid (Marsilid®), developed for the treatment of tuberculosis, and the drug was later released for clinical use as an antidepressant agent. The development of meprobamate (Miltown®), an approved treatment for anxiety, evolved from initial efforts to find a chemical that would inhibit the enzymatic destruction of the antibiotic drug penicillin. The psychiatric uses of lamotrigine (Lamictal®) and vagus nerve stimulation were prompted by initial observations that epilepsy patients receiving these treatments had positive mood effects. Nurses should be familiar with the concept of serendipity, as they often are in the best position to observe, record, and report on unexpected clinical effects in patients taking any kind of prescription or nonprescription medication.
The concept of serendipity in drug discovery implies the finding of one thing while looking for something else (Ban, 2006). In two previous articles, I described how the development of drugs and devices for use in psychiatry followed from initial serendipitous observations.

**CHLORPROMAZINE**

Chlorpromazine (Thorazine®), a drug containing a phenothiazine chemical nucleus, is an approved treatment for schizophrenia and bipolar mania. Phenothiazine is an organic chemical compound first synthesized in 1883 and used as a treatment for parasitic worms (Ban, 2006). Promethazine (Phenergan®), a drug with a central phenothiazine chemical structure, was synthesized in the early 1940s. It was found to have prominent antihistamine properties. For this reason, the surgeon Henri Laborit used promethazine for the prevention of surgical shock. He reported in 1949 that when the drug was given prior to surgery, patients remained calm, mildly sedated, and relaxed. In response to a request from Laborit for a drug similar to promethazine that might attenuate anxiety and potentiate anesthesia, chlorpromazine was synthesized in 1950 and released for clinical investigation in 1951. Clinical investigations of chlorpromazine in surgical patients by Laborit and colleagues found that the drug did not cause a loss of consciousness or a change in mentation, but produced a tendency to sleep and a disinterest in the patients’ surroundings. In the report published in 1952 describing these observations in surgical patients, Laborit, Huguenard, and Alluaume also commented on the possible use of chlorpromazine for psychiatric patients. Several other reports were published later in 1952 describing the use of chlorpromazine in France, specifically for psychiatric patients with psychotic symptoms. Chlorpromazine became available by prescription in France in November 1952, and worldwide use of the drug commenced in 1953.

**IPRoniaZID**

Iproniazid (Marsilid®) is a hydrazine drug synthesized in 1951 for the treatment of tuberculosis (Bloch, Dooneief, Buchberg, & Spellman, 1954). In 1952, a report describing the use of the drug in tuberculosis noted that some patients became euphoric and overactive (Selikoff, Robitzek, & Orenstein, 1952). On the basis of this observation, two groups of investigators independently conducted clinical studies of iproniazid in patients with depression. The therapeutic effectiveness of the drug for depression was first reported in 1957 (Crane, 1957; Loomer, Sanders, & Kline, 1957), and it was released for clinical use as an antidepressant agent in 1958. Although the monoamine oxidase inhibitor (MAOI) property of iproniazid was discovered in 1952, the antidepressant effect of the drug was not attributed to the MAOI property until the late 1950s. Because of frequent reports of hepatitis occurring in patients taking iproniazid, it was withdrawn from clinical use in 1961. Other safer hydrazine MAOI drugs were developed and marketed as antidepressant agents, such as isocarboxazid (Marplan®) in 1959 and phenelzine (Nardil®) in 1961.

**Mepробamate**

Meprobamate (Miltown®), an approved treatment for anxiety, was the first drug discovered that ushered in the era of tranquilizer drugs and other antianxiety medications (Ban, 2006). The development of meprobamate evolved from initial efforts to find a chemical that would inhibit the enzymatic destruction of the antibiotic drug penicillin. Penicillin was first discovered in 1928, but its clinical use as an antibiotic agent did not become widespread until the early 1940s. Frank Berger, a microbiologist working in the United Kingdom during World War II, was looking for a substance that would preserve penicillin by inhibiting penicillinase-producing bacteria. One of the substances he tested, mephenesin (Myanesin®), first synthesized in 1908, had the effect he was looking for. While performing toxicity studies in laboratory animals, Berger noted that mephenesin...
produced tranquilization, muscle relaxation, and a mild somnolence from which animals could be easily roused. These findings were published by Berger and Bradley in 1946, and the drug was released in 1948 for clinical use for muscle relaxation during light anesthesia.

Besides its use during anesthesia, mephenesin was not otherwise clinically useful because it was rapidly metabolized and had a very short duration of action. Further investigation determined that the drug’s rapid deactivation was blocked by carbamate chemical compounds. Of the hundreds of carbamate compounds synthesized, meprobamate (discovered in 1950) had a significantly longer duration of action than mephenesin but with similar tranquilizing properties. Additional clinical trials were conducted, and the therapeutic effect of meprobamate in anxiety and tension states was first reported in 1955. The drug was then released for clinical use later that year. Meprobamate became extremely popular during the late 1950s and early 1960s, before being supplanted by benzodiazepine medications and other tranquilizing drugs.

**LAMOTRIGINE**

The anticonvulsant drug lamotrigine (Lamictal®), an approved treatment for epilepsy and bipolar disorder, was originally synthesized in the early 1980s as part of a rational drug discovery program for new anticonvulsant drug treatments (Weisler et al., 2008). At the time lamotrigine was first synthesized, no new drugs had been successfully developed for the treatment of epilepsy for more than 3 decades. Human Phase I clinical studies of lamotrigine were conducted in the early 1980s, followed by a series of pivotal clinical trials. The first approval for the use of lamotrigine in epilepsy was in 1990 in Ireland, followed by worldwide regulatory approvals for epilepsy over the next few years. In December 1994, lamotrigine was approved for use in epilepsy in the United States.

During the early epilepsy clinical trials, improved mood and communicativeness was observed in patients receiving lamotrigine (Smith, Baker, Davies, Dewey, & Chadwick, 1993). The first use of lamotrigine in two patients with bipolar disorder was reported at the May 1994 annual meeting of the American Psychiatric Association, prior to the drug’s U.S. approval for epilepsy later that year. The idea to try lamotrigine in bipolar disorder was based on the clinical mood effects of lamotrigine observed in the epilepsy trials (Smith et al., 1993), as well as theoretical considerations about the potential utility of anticonvulsant drugs in bipolar disorder (Ballenger & Post, 1978). For use in these two patients, lamotrigine was imported from Europe under a U.S. Food and Drug Administration (FDA) compassionate use exemption. Clinical trials conducted in the United States from 1995 to 2001 ultimately led to its approval as a maintenance treatment for bipolar disorder in 2003.

**VAGUS NERVE STIMULATION**

Vagus nerve stimulation (VNS) was approved for the treatment of refractory epilepsy in 1997 and for chronic treatment-resistant depression in 2005 (Howland, 2006a, 2006b). During the early epilepsy trials of VNS, at follow-up visits at the Gainesville, Florida study site, patients frequently stayed in the same hotel. A hotel clerk reported to one of the VNS investigators that the VNS patients seemed to be in better spirits as time passed (Park, Goldman, Carpenter, Price, & Friehs, 2007).

Anecdotal reports of mood improvements, apparently unrelated to reduction in seizure frequency, further inspired the VNS investigators to systematically assess mood and anxiety symptoms in patients with epilepsy (Elger, Hoppe, Falkai, Rush, & Elger, 2000; Harden et al., 2000). Both retrospective data analysis and prospective assessments during epilepsy trials suggested that VNS was associated with reduction in depressive symptoms, even in the absence of improvement in seizures. Furthermore, the improvement in seizure frequency in the VNS group was not related to the improvement in mood for the individuals, suggesting that VNS may improve mood independent of improvement in seizure frequency. These obser-
vations led to the clinical trials that resulted in FDA approval of VNS for chronic treatment-resistant depression.

CONCLUSION

Serendipity is one of many factors that have contributed to the discovery of the psychotropic effects of various drugs. This is especially true of some of the first drugs used in psychiatry. Modern drug development has moved toward the rational design of drugs, based either on known or suspected pathophysiological abnormalities in mental disorders or on similarities to existing effective drug therapies (Klein, 2008). However, there will always be an important role for serendipitous observations or findings, which can prompt the investigation of new uses of existing psychotropic drugs or the novel use of non-psychotropic drugs that might have clinical applications for the treatment of mental disorders.

Nurses should be familiar with the concept of serendipity, as they often are in the best position to observe, record, and report on unexpected clinical effects in patients taking any kind of prescription or nonprescription medication. However, chance alone or pure luck is not likely to lead to important or relevant observations. Louis Pasteur has been famously quoted as saying that “in the fields of observation chance favors only the prepared mind” (Ban, 2006). A prepared and open mind is usually required to recognize the importance of accidental or unexpected observations (Jest, Gillin, & Wyatt, 1979). For nurses, this means that broad clinical experience and a solid working knowledge of clinical pharmacology are necessary ingredients for serendipity to occur.

REFERENCES


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