Chapter 3: The Pharmacological Treatment of Anxiety Disorders across the Lifespan

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History of the Pharmacological Treatment of Anxiety

The history of the pharmacological treatment of anxiety is both long (millennia), incredibly short, and continuing. For millennia, naturally occurring herbal substances (e.g., valerian, laudanum, and kava kava) and fermentation-derived alcohols (ethanol) have been used for amelioration of anxiety. For example, in Genesis (9:20-21), Noah planted a vineyard, drank of the fermented wine, became drunken, and he was lying uncovered in his tent. While drunkenness was a "sin", moderate doses were anxiolytic and presumably socially acceptable. Thus, alcohol, along with several bromide preparations, chloral hydrate, and paraldehyde were classically used to treat anxiety; however, the adverse societal and medical consequences of such use no longer support this as a medical approach. Self-medication with alcohol as an anxiolytic, however, continues.

The next step in the pharmacological treatment of anxiety was the development of the barbiturates in the early 1900s and the marketing of phenobarbital in 1914. All the marketed barbiturates (there were at least 50) were used from about 1915-1960 as anxiolytics as well as sedatives, hypnotics, anticonvulsants, and anesthetics. All barbiturates induce sedation as well as profound psychomotor impairments. They are also lethal in overdose, leading to remaining and very controversial medical uses in physician-assisted suicide and in lethal injection procedures.

In the early 1950s, attempts were made to identify sedative drugs that were safer (less lethal in overdosage) than the barbiturates. This led in two directions: first were the less sedating anticonvulsants (e.g., diphenylhydantoin and others) and second were the non-barbiturate anxiolytics/hypnotics. The latter included meprobamate (Equanil, Miltown), carisoprodol (Soma), glutethamide (Doriden), methyprylon (Noludar), ethchlorvynol (Placidyl) and, in the

early 1970s, methaqualone (Quaalude). These drugs all attempted to provide anxiolysis with less hypnotic action, less lethality in overdose, and less potential for psychomotor impairment and physical dependence. In general, such goals were not met and their use today is rare. One exception is carisoprodol (which is metabolized to meprobamate) that is frequently prescribed, yet somewhat inappropriately, as a "muscle relaxant"; it is also a commonly encountered drug of abuse and intoxicant.

A landmark in anxiolytic history was the introduction of the *benzodiazepine tranquilizers* [e.g., diazepam (Valium) and chlordiazepoxide (Librium)] in the early 1960s followed by many others throughout that decade. Their claim-to-fame was that they were relatively non-fatal in overdosage and presumably less sedating. This enhanced safety led to incredible popularity and widespread use that continues today. Uses include treatment of anxiety, epilepsy, alcohol withdrawal, insomnia, agitation, muscle tension, and even to provide amnesia for certain types of medical/dental procedures under the term "conscious sedation." Unfortunately, benzodiazepines retain the cognitive-impairing effects, the psychomotor impairments, and the dependence inducing and "addicting" characteristics of the barbiturates. Because of the adverse cognitive effects of the benzodiazepines, their use in the young and the elderly has become relatively contraindicated (learning impairments in the young and dementing and extreme psychomotor effects in the elderly).

At about the same time that the benzodiazepines were being introduced into medicine, chlorpromazine (Thorazine) and several other *phenothiazine tranquilizers* were identified and introduced for the treatment of schizophrenia. The phenothiazines induced a state of *neuroleptic tranquilization* and anxiolysis, but this was accompanied by serious side effects including parkinsonian-like movements and a "neuroleptic state" characterized by reduced activity,

lethargy, and impaired motor control. These neuroleptic tranquilizers reduced confusion, delirium, delusions, hallucinations, anxiety, and psychomotor agitation in psychotic persons.

To differentiate the phenothiazines from the benzodiazepines the former were referred to as *major tranquilizers* and the latter as *minor tranquilizers*. The major tranquilizers were not clinically used to treat anxiety (except in schizophrenic patients), so the minor tranquilizers dominated the treatment of anxiety until the late 1980s when fluoxetine (Prozac), the first serotonin-specific reuptake inhibitor (SSRI), was marketed as an antidepressant/anxiolytic. Fluoxetine (and five additional SSRIs to follow in the 1990s) differentiated themselves from the barbiturates and the benzodiazepines in that they were not fatal in overdosage and exerted a much lower degree of cognitive inhibition. Indeed, as depression and anxiety were relieved, a degree of cognitive enhancement can be observed.

Importantly, as the SSRIs were being marketed as antidepressants/anxiolytics, the "atypical antipsychotic" drugs were almost simultaneously being developed for treating schizophrenia and bipolar disorder; these drugs were relatively devoid of the neuroleptic properties displayed by the older "major tranquilizers", at least at therapeutic doses. Among their many clinical uses, the atypical antipsychotic drugs possess useful anxiolytic properties for use in "resistant" anxiety states (Julien et al, 2011). Indeed, atypical antipsychotics have been utilized in the treatment of multiple types of anxiety disorders including treatment resistant post-traumatic stress disorder (PTSD) (Ahern et al, 2011). However, the evidence is less clear for military service-related PTSD (Krystal et al, 2011).

Next, several of the newer antiepileptic drugs (in addition to possessing anticonvulsant properties) have been shown to possess important anxiolytic properties. Specifically, they have

been shown to be useful in the treatment of such disorders as social anxiety (Feltner, et al, 2011) and the nightmares and sleep disruptions associated with PTSD (Ahern, et al., 2011).

Finally, certain medications used clinically to lower blood pressure in patients with hypertension are successfully used for certain anxiety states. For example, propranolol (Inderal) has long been used to reduce performance anxiety and prazosin (Minipres) has been recommended for the treatment of PTSD-associated nightmares (Aurora, 2010).

In summary, anxiety disorders today are being medically treated with drugs of many classes, including:

- Benzodiazepines, such as alprazolam (Xanax), lorazepam (Ativan), clonazepam (Klonopin), and diazepam (Valium)
- Antidepressant/anxiolytic SSRIs and the serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine (Effexor) and duloxetine (Cymbalta)
- Atypical antipsychotics, such as quetiapine (Seroquel), risperidone (Risperdal), and aripiprazole (Abilify)
- Antiepileptic drugs, such as gabapentin (Neurontin), pregabalin (Lyrica), lamotrigine (Lamictal), and topiramate (Topamax)
- Certain antihypertensive medications that either slow heart rate (e.g., propranolol) or relax arterial blood vessels (prazosin)

All of this allows the treatment provider a range of prescription options never before available with which to taper medication to an individual's particular needs and balancing therapeutic efficacy with potential side effects that might be inappropriate for individual patients. The remainder of this chapter will focus on medication selection for the treatment of anxiety

disorders in persons from the intrauterine state, through childhood and adulthood, and into their elderly years.

Treatment of Anxiety in the Neonate

There is increasing evidence that untreated anxiety and depressive disorders in pregnant women are associated with adverse outcomes in the newborn infant. This link between maternal disease and early appearance of symptomatology in the newborn seems to be due to environmental processes, independent of inherited effects (Gleason et al, 2010; Lewis, et al, 2011). By inference, treating anxiety during pregnancy should lead to improvements in pregnancy outcomes, benefiting the longer-term mental health of the offspring. Therefore, the susceptibility to future states of anxiety (and depression) begins even before birth. The overall goal of treating early onset anxiety (even neonatal) is to reduce the severity of current anxiety symptoms in the pregnant female and ultimately, to prevent the long-term consequences of untreated anxiety in offspring. Obviously, we do not know whether or not a neonate can experience anxiety symptom; but we are learning that untreated maternal anxiety disorders has profound effects on the developing brain of a neonate.

Multiple approaches are needed to reduce anxiety in pregnant women. Treatments involve resolving nutritional deficiencies, to psychosocial interventions, to pharmacological intervention. Here, we focus on pharmacological interventions, although nutrition will be briefly addressed.

Can a neonate suffer from anxiety? No one knows; but untreated maternal anxiety sets the stage for reduced developmental scores in the newborn, slowed mental development, and potentially the future development of anxiety and depressive disorders in the young child. This is consistent with the work of Luby (2009), Luby et al. (2009), Luby (2010), and Rao (2010)

who demonstrated that depression in preschool children (as young as 3-years of age) is correlated with untreated depression and anxiety in the pregnant mother and is associated with abnormal development of neurons within the hippocampus of the newborn. This may potentially increase their susceptibility to early age depressive and anxiety disorders. Why might the prenatal infant brain be so vulnerable during prenatal development? As stated by Agin (2010, p. 57):

> "It is estimated that in the developing brain and nervous system of the prenatal human, about 250,000 new neurons are generated each minute at the peak of cell proliferation during gestation."

Therefore, the prenatal treatment of the long-term childhood anxiety outcomes lies in treating anxiety in the pregnant mother. Such stress can result in poor compliance with prenatal care, exposure to drugs of abuse, alcohol, and cigarettes, and disruptions in the home environment. All adversely affect the fetal environment. The overall goal is to reduce the mother's levels of stress hormones and restore nutritional deficiencies necessary for normal development of the fetal brain. In the developing fetal brain, stress hormones, certain vitamin deficiencies, and deficiencies in omega-3-fatty acids all adversely affect neurogenesis and migration programming.

Pharmacological treatment of anxiety in the mother involves consideration of adverse effects of medications on organ development (teratogenesis) in the infant and in long-term medication-related neurobehavioral outcomes. Despite decades of study, data remains controversial and conflicting. However, with some positive reports of adverse structural deficits, most hold that benzodiazepines should likely be avoided during the first trimester of pregnancy. Since pregnancy is unplanned in about 50% of pregnancies, these women are unaware that they are pregnant for several weeks following conception. It is therefore wise to avoid

benzodiazepine therapy in women who could potentially become pregnant and therefore expose a young fetus to undesired drug effects. Also of consideration are residual drug effects and withdrawal symptoms in children born of a female taking benzodiazepines until the time of delivery.

Regarding SSRI-type antidepressants/anxiolytics, these medications in humans do not appear to increase the risk of congenital anomalies. One possible exception is paroxetine (Paxil), which has been associated with a slight increase in cardiac anomalies. Importantly, the mother should likely be exposed to only one medication as polypharmacy increase risk substantially (Kornum et al, 2010). Fluoxetine has perhaps the widest margin of safety, but likely should be withdrawn several weeks before delivery to minimize SSRI withdrawal signs in the newborn.

Neurodevelopmental effects in children exposed to SSRIs *in utero* remains controversial. No major adverse effects have been reported, although recent research (Croen et al, 2011) indicates a potentially small increase in the incidence of autism spectrum disorders. It is agreed, however, that if such a risk occurs, it is unlikely to be a major risk factor for these disorders.

Regarding anticonvulsant drugs as anxiolytics during pregnancy, in general these should be avoided, posing a much more serious teratogenic risk (Grover et al, 2006). If necessary, lamotrigine (Lamictal) appears to have the greatest safety ratio of available anticonvulsants.

Atypical antipsychotic drugs are widely used by women of childbearing age for multiple disorders including treatment of bipolar disorder, depression, and anxiety. Exposure to one of these drugs is therefore quite likely in many women who may become pregnant. While much remains to be learned, in February 2011 the FDA issued class warnings for atypical antipsychotic use during pregnancy, advising of abnormal muscle movements and withdrawal signs in

offspring whose mothers received these drugs during pregnancy. The potential teratogenicity of atypical antipsychotic drugs taken by women during pregnancy is little studied.

In summary, at this point, SSRIs appear to be among the safest medications for treatment of anxiety during pregnancy (perhaps avoiding paroxetine in the first trimester).

Treatment of Preschool Anxiety

Anxiety disorders during the preschool period (ages 3-5 years) is common, with social anxiety, generalized anxiety, separation anxiety, and specific fears leading the list of such disorders (Edwards et al, 2010). Further, these disorders have a years-long stability, potentially affecting the developing person to predisposion to anxiety disorders as young adults. Therefore, aggressive treatment of preschool aged children is necessary, not only to control current problems, but also to prevent progression to disorders in subsequent years. These youngsters will not "grow-out" of their disorder [Gleason et al (2007); Fanton and Gleason (2009)].

For non-PTSD and non-OCD anxiety disorders in preschoolers, behavioral therapy techniques and cognitive therapies are valuable (Hirshfeld-Becker, et al, 2011). Treatment is continued for at least three months before considering medication. Parental psychiatric assessment may be valuable and necessary. For non-PTSD and non-OCD anxiety disorders in preschoolers, the entire pharmacological literature comprises only a handful of case reports. Fluoxetine may be the first choice for pharmacological treatment of preschool anxiety, but this is based only on empirical evidence. A discontinuation trial after six to nine months of therapy has been recommended. Benzodiazepines are not recommended because of possible cognitive impairments and subsequent learning difficulties. The only exception to this might be for the ultra-short-term treatment for dental anxiety.

PTSD is common in preschoolers and difficult to treat (DeYoung et al, 2011). Psychotherapeutic interventions are the treatments of choice (Kowalik et al, 2011). As stated by Julien et al (2011, page 604):

> "The experts do not endorse medication; however, according to surveys, only 11% of providers reported that they *did not* use medication for preschool PTSD. Here, experts differ from practitioners. Again, benzodiazepines are not recommended."

There is little research on OCD in preschoolers. Psychoeducation, cognitive therapies, and exposure therapies are effective. SSRIs may be effective and can be combined with cognitive therapies. SSRI therapy probably should be considered as the treatment of last resort and SSRI treatment should always occur in the context of ongoing cognitive and/or behavioral interventions.

It is important to note that certain preschool disorders (such as ADHD) may be treated with dopaminergic compounds such as amphetamine (Adderall) and methylphenidate (Ritalin). Any medications that act by increasing brain dopamine levels may induce or worsen anxiety disorders. Often such anxiety is treated by adding an anxiolytic, rather than discontinuing the stimulant and reevaluating the situation. In its use in adults with depression, bupropion (Wellbutrin) can cause an identical effect.

Treatment of Anxiety in School-Age Children & Adolescents

Anxiety disorders are common in school-aged children and adolescents and cause substantial impairments in school, in family relationships, and in social functioning. Such disorders are among the earliest psychiatric conditions to manifest, with a median age of onset of 11 years (Ramsawh et al, 2010). Anxiety disorders in youth also predict adult anxiety disorders,

substance abuse, and major depression. A reasonable estimate of the occurrence of any anxiety disorder during adolescence is about 13% with a prevalence rate in children under 18-years at 5.7 to 12.8%. Bridge and coworkers (2007), in a large meta-analysis, found considerable therapeutic efficacy of antidepressant medications in treating anxiety disorders in children and adolescents. Indeed, it is now generally agreed that psychotherapy and pharmacotherapy are effective in improving clinical impairments from anxiety disorders and maintaining these improvements (Kodish et al, 2011; Rynn et al, 2011).

With increasing recognition of childhood anxiety as a serious illness with potentially life-long consequences, interest has risen about the use of psychopharmacologic interventions. On the other hand, this has been accompanied by concern over potential overdiagnosis, overtreatment of youths (Correll et al, 2011), and potential for medication-induced suicidal thoughts or actual suicides. Regarding suicidality with SSRIs, anxiety alone does not appear to be a predictive factor; however, these medications can at the beginning of administration as monotherapy can have pro-suicidal effects in patients with hints of suicidality or suicidal behavior, by increasing the intensity of already present suicidal predictors, such as dysphoria, impulsiveness, agitation, and so forth. If depression is suspected, appropriate diagnosis and interventions should be undertaken before SSRI treatment is initiated.

In clinical trials, generalized anxiety disorder, separation anxiety, and social phobia are often grouped together because of a high degree of symptom overlap, their distinction from other anxiety disorders, and their similar response rates compared with OCD and PTSD. Research suggests that both CBT and SSRIs are effective in the treatment of these anxiety disorders in children and adolescents. Indeed, CBT and SSRIs seem to be equally efficacious in treatment. Furthermore, combination treatment (CPT plus an SSRI) may be more efficacious than either

treatment alone. For example, Walkup and coworkers (2008) found that 81% of children with anxiety disorders receiving both sertraline (Zoloft) and CBT were classified as responders, vs. 60% with CBT alone, 55% for sertraline alone, and 23% for placebo medication (Figure 3.1). The authors concluded that:

> "CBT alone, sertraline alone, and the combination are all efficacious short-term treatments. Combination therapy is the most efficacious and provides the best chance for a positive outcome. Any of the three can be recommended, taking into consideration the family's treatment preferences, treatment availability, cost, and time burden." (Page 2762).

As reviewed by Connolly and coworkers (2011):

> "CBT has been extensively studied and has shown good efficacy in the treatment of childhood anxiety disorders. A combination of CBT and medication may be required for moderate to severely impairing anxiety disorders and may improve functioning better than either intervention alone. SSRIs are currently the only medications that have consistently shown efficacy. Despite this, the availability of CBT in the community is limited. Current research is focusing on early identification of anxiety disorders in community settings, increasing the availability of evidence-based interventions, and modification of interventions for specific populations." (Page 99)

Obsessive-compulsive disorder (OCD) is now estimated as the fourth most common psychiatric disorder in adolescents, with an incidence of 2-3.6%. Pharmacotherapy with SSRIs is usually indicated as part of multimodal therapy. As stated in a recent POTS II study (Pediatric OCD Treatment Study II) (Franklin et al, 2011):

> "Partial response to SSRIs is the norm and augmentation with short-term OCD-specific CBT provides additional benefit (Franklin et al, 2011); 68% of OCD youths receiving medication management plus CBT strategy were considered responders, which was superior to 34% in the CBT group and 30% in the medication-only group" (Figure 3.2). (Page 1224).

From the earlier POTS I study, only about 3.6% would be expected to respond to placebo therapy (Pediatric OCD Treatment Study (POTS) Team, 2004).

Despite these positive results, perhaps 30% of youth with OCD will be resistant to SSRI plus CBT therapy. Augmentation strategies are therefore necessary. Here, a focus has been on the use of atypical antipsychotics in such youth. At this early stage of research, both quetiapine (Seroquel) and aripiprazole (Abilify) have reported efficacy (Mohr et al, 2002; Masi et al, 2010). In the Masi and coworkers study, 39 adolescents (mean age 12 years) were titrated to a final dose of 12 mg of aripiprazole per day and the drug was effective in more than 50% of patients resistant to continuing SSRI therapy. For a recent analysis of this literature see the Brown University Child & Adolescent Psychopharmacology Update (2011).

Post-Traumatic Stress Disorder (PTSD) is relatively common in children and adolescents, often as a result of early age traumas. Despite this, little has been reported on the efficacy of pharmacological interventions. A recent practice parameter for child and adolescent PTSD includes little on psychopharmacologic treatment. Strawn and coworkers (2010) performing a meta-analysis of published literature noted that the data do not support the use of SSRIs as first-line treatments for PTSD in children and adolescents. For example, sertraline (Zoloft) was ineffective in a placebo-controlled study in 131 youths (6-17 years) with PTSD (Robb et al,

2010). Limited evidence notes that atypical antipsychotics and several mood stabilizers may attenuate some symptoms, such as intrusive thoughts. Antiadrenergic agents (e.g., clonidine, guanfacine, prazosin) can reduce symptoms such as hyperarrousal, intrusive symptoms, and impulsivity. Other medications may be needed to target various associated PTSD symptoms such as depression, affect instability, disruptive behavior, and dysregulated attachment.

Again, it must be stated that cognitive inhibitors are not indicated for use in children and adolescent. This greatly limits the use of benzodiazepines and tricyclic antidepressants.

Treatment of Anxiety in Adults

As listed above, multiple classes of medications are used to treat anxiety disorders in adults. These included benzodiazepines, antidepressant/anxiolytic SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antipsychotics, and certain antiepileptic drugs. Other compounds occasionally encountered include medications that blunt the tachycardic response to anxiety (beta blockers and calcium channel blockers), antihypertensive drugs that dilate blood vessels (prazosin) and certain antihistamines [e.g., hydroxyzine (Vistaril)].

Benzodiazepines

For 50 years, benzodiazepines formed the mainstay of anxiety treatment. Their efficacy and immediacy of response is their primary advantage. This, however, is offset by cognitive impairments (tolerable to debilitating), addicting properties, and withdrawal complications (sleep disruptions to fatal seizures). Other side effects include sedation, hypnosis , and anterograde amnesia (the extreme of cognitive dysfunction).

Because of these side effects, benzodiazepines today may be more properly classified as sedative-hypnotic drugs rather than anxiolytics, the latter term implying some sort of specific

effect to ameliorate anxiety separate from general depression of the CNS. Of note, the depressant effects of benzodiazepines is additive with the action of ethanol, causing further impairment in psychomotor skills.

The adverse cognitive effects of benzodiazepines are insidious and often missed in clinical practice. The reason for this is the long half-lives of these drugs, almost all of which exceed the usually prescribed dose intervals. For example, several benzodiazepines are metabolized to a long-acting active intermediate (nordiazepam) that has a half-life of several days. Others considered to be shorter acting have half-lives of 12-14 hours (alprazolam, temazepam, lorazepam), or more than 24 hours (clonazepam). Only triazolam (half-life of 2.5 hours) and midazolam (half-life of about 1.5 hours) have a rapid onset and noticeable cessation of action. When a drug with a half-life of greater than 12 hours is administered every 6-8 hours, one is never "drug-free." As a result, even professionals seeing these persons rarely notice drug-induced impairments. Even if the benzodiazepine is taken only at bedtime for sleep, residual daytime impairment will persist and some drug remains when the next bedtime dose is taken (leading to drug accumulation and even more impairment).

Clinical uses still appropriate for benzodiazepines may include: (1) intentional anterograde amnesia [midazolam (Versed)]; rapid onset of sleep [triazolam (Halcion)]; perhaps the short-term treatment of debilitating anxiety [alprazolam (Xanax), clonazepam (Klonopin), lorazepam (Ativan)]; perhaps short-term use in event-driven emotional distress; and the prevention of seizures in alcohol withdrawal [chlordiazepoxide Librium)]. Regarding the latter, antiepileptic drugs such as gabapentin (Neurontin) and pregabalin (Lyrica) may be viable options. Clonazepam, alprazolam, and lorazepam are commonly prescribed today for the

treatment of anxiety; however, efficacy is limited, tolerance and dependence are problematic, and cognitive dysfunction is often underappreciated and poorly recognized.

Antidepressants

Most antidepressants (with the notable exception of bupropion) exert anxiolytic actions as well as antidepressant actions. This is fortunate because of the common occurrence and comorbidity of depression with one or more anxiety disorders. Whether such common actions are a result of potentiation of either (or both) serotonin and norepinephrine neurotransmission (by reuptake blockade) remains unclear. The *tricyclic antidepressants* (TCAs) were introduced into medicine about 50 years ago, blocking both norepinephrine and serotonin reuptake (the original *dual action* antidepressants). These drugs have anxiolytic properties, but side effects limit their use. Such side effects include sedation, cognitive impairments, delirium and other signs of histaminic and cholinergic receptor blockade. These medications are also potentially fatal in overdose. Today, their use is generally restricted to situations where other, safer medications are unaffordable. Clomipramine (Anafranil) is a TCA approved long ago for the treatment of OCD (the first FDA approval of an antidepressant for treatment of an anxiety disorder). Its use for treatment of OCD remains.

Modern versions of dual acting antidepressants that block norepinephrine and serotonin reuptake include venlafaxine (Effexor), desvenlafaxine (Pristiq, the active metabolite of venlafaxine), duloxetine (Cymbalta), and milnacepram (Savella). In general, these three medications act through the same mechanisms of action as the TCAs except that they lack the antihistaminic and anticholinergic properties of the TCAs. All three share antidepressant/anxiolytic/analgesic actions, making them particularly useful in the treatment of disorders where 2 or all 3 actions are desired (e.g., in the treatment of fibromyalgia and chronic

pain conditions). Of particular note, these medications are useful in the treatment of generalized anxiety disorder (venlafaxine is FDA approved for such use), panic disorder (Serretti et al, 2011), panic disorder with agoraphobia (Chen and Liou, 2011), and as an alternative to SSRIs in the treatment of obsessive-compulsive disorder (Sansone and Sansone, 2011). Duloxetine may be more effective in reducing anxiety than is venlafaxine (Serafini et al, 2010), although no definitive explanation can be offered for this observation. With these three medications, one must be aware of potential "switching" from depression to hypomania and mania with adverse consequences (Gao et al, 2008; Chen et al, 2010).

Anticonvulsants

Certain anticonvulsants have long been utilized in the management of chronic pain syndromes, including the pain associated with peripheral neuropathies. More recently, their anxiolytic properties have been elucidated, reducing the amygdalar activation during anticipation of emotional images (Aupperle et al, 2011). Most studied is the use of pregabalin (Lyrica) for generalized anxiety disorder (Boschen, 2011) and social anxiety disorder (Feltner et al, 2011. An older and closely related drug, gabapentin, is less expensive and likely similarly effective. The less sedating anticonvulsant/antidepressant medication, lamotrigine (Lamictal), may similarly reduce anxiety (Sepic-Grahovac et al, 2011). Topiramate (Topamax) also has anxiolytic properties, but its use is limited by clinically significant cognitive difficulties. Anastassiou and coworkers (2011) recently wrote:

> "Significant reductions in pain and pain-related sleep interference, combined with reductions in feelings of anxiety and depression, suggest that pregabalin under real-world conditions improved the overall health and well being of patients with neuropathic pain." (Page 417)

Atypical Antipsychotics

As stated earlier, traditional (first generation) antipsychotic drugs reduce the symptoms of schizophrenia accompanied by emotional tranquilization, calming, and anxiolysis. Adversely, these effects could not be achieved without the accompanying movement disorders and induction of the "neuroleptic state." The claim to fame of newer, second generation or "atypical" antipsychotics is that relief of symptoms of schizophrenia could be achieved at doses, which did not necessarily have these accompanying movement and neuroleptic side effects. This rapidly led to exploration of uses outside of the treatment of schizophrenia. Such uses included treatment of bipolar disorder, autism spectrum disorders, behavioral agitation and aggressive disorders, anger disorders, and (more recently) depression and anxiety disorders. Indeed, two of these atypical antipsychotics, aripiprazole (Abilify) and quetiapine (as Seroquel-XR), are FDA approved as either mono-therapy or as augmenting agents in the treatment of depression. "Off-label" these medications (especially quetiapine and aripiprazole) are being widely used as effective medication either in mono-therapy or combination therapy in the treatment of generalized anxiety disorder, OCD (Vulink et al, 2011; Maher et al, 2011; Katzman, 2011) and PTSD (Ahearn et al, 2011; Krystal et al, 2011).

Side effects of atypical antipsychotics are significant and can limit therapeutic utility. These include weight gain (with risperidone and occasionally with quetiapine), a potential for early-onset diabetes mellitus, sedation (with risperidone and quetiapine), elevated blood lipids, akathisia (with aripiprazole), and occasional extrapyramidal signs. Because of this potential, most practitioners begin therapy of anxiety disorders with an SSRI, reserving atypical antipsychotics for "failed" or SSRI-resistant cases. Atypical antipsychotics have the advantage

of more rapid onset of effect, less sexual dysfunction, and improved mood stability, for example in anxious depression (Rao and Zisook, 2009; Gao et al, 2009).

Treatment of Anxiety in the Elderly

There is a paucity of research on the treatment of anxiety in older people, although the availability of several new assessment scales suggests increased interest in this topic. Indeed, anxiety disorders are common. Likely, such anxiety is disruptive and frequently overmedicated in order to achieve behavioral control. There is also a potential for worsening of any existing cognitive impairment. This applies especially to the administration of benzodiazepines to elderly persons.

Benzodiazepines

One quarter of the prescription drugs sold in the United States are used by the elderly, often for chronic pain, insomnia, and anxiety. Of available drugs, benzodiazepines continue to be used in this population, both for treating anxiety and insomnia. While this was perhaps condoned in past years, today it is felt that benzodiazepines should be rarely, if ever, prescribed in this population (Manthey et al, 2011). Many patients treated with benzodiazepines should be withdrawn and therapeutic strategies, other than benzodiazepines, should be considered to treat anxiety and insomnia in these patients (Bourin, 2010). Why such strong words?

- First, benzodiazepines have well described adverse cognitive effects, either worsening pre-existing dementia or inducing *de novo* dementia that is reversible with drug discontinuation.
- Second, benzodiazepine use in the elderly is associated with an increased incidence of falls with debilitating hip fractures.
- Third, problems posed by the elderly operating motor vehicles are potentiated by use of benzodiazepines in the elderly.

- Fourth, many elderly consume alcohol, and benzodiazepine use with alcohol produces remarkable cognitive dysfunction and behavioral risks.
- Fifth, withdrawal is difficult, with a risk of seizures, insomnia, and rebound increases in anxiety and agitation.

Antidepressants

SSRIs are currently the drugs of choice for treating anxiety in the elderly. Use of the tricyclics (TCAs) is severely limited by cognitive impairments and possibly anticholinergic delirium. Lenze and coworkers (2011) studied escitalopram (Lexapro) in the treatment of generalized anxiety disorder in adults older than 60 years. They noted that the drug reduced peak and total cortisol levels in the brain and these reductions paralleled reductions in anxiety. Likely, all SSRIs share these actions. Doses should likely be started at low levels and advanced slowly.

Since elderly frequently take multiple prescribed medications (20-40% of elderly take 8 or more medications), the potential for drug interactions is real. SSRIs inhibit the activity of multiple drug-metabolizing enzyme systems. The result of such inhibition is reduced metabolic breakdown of other medicines taken by these patients. This reduced metabolism results in marked increases in the blood concentrations of other drugs; sometimes even doubling these concentrations, often resulting in dangerous situations. For example, increasing the blood concentration of blood thinners (anticoagulants such as warfarin) may lead to fatal hemorrhage. SSRIs can also inhibit the breakdown of many opioid analgesics, with methadone being the most susceptible (Tennant, 2010).

Recently, duloxetine (Cymbalta) has been reported to be effective in treating elderly patients suffering from comorbid depression, anxiety, and chronic low back pain (Karp et al, 2010).

For elderly suffering from comorbid insomnia, anxiety, and depression, mirtazapine (Remeron) has proved very effective. It is equally effective as the SSRIs, and improves sleep quality with bedtime use (Croom et al, 2009). Its side effect of increasing appetite with modest weight gain may be of benefit in this population. Its use as a nighttime sleep aid has not been accompanied by an increase in falls and fractures (Coupland et al, 2011).

Atypical Antipsychotics

For as long as the traditional antipsychotics have been available, they have been used to calm agitated and aggressive behaviors in the elderly. This type of chemically-induced behavioral control has always been ethically controversial, often appropriately so. A need has remained for superior medications to treat this common disorder in elderly who exhibit difficult behaviors.

Since their introductions in the 1990s, the atypical antipsychotic medications have become the standard of care for behavioral and psychological symptoms of dementia and to control agitated, anxious, and aggressive behaviors in the elderly. This is said despite warnings from the FDA about potential adverse reactions possibly associated with such use (discussed below). Today, following increases in such use, reductions to more acceptable and reasonable levels of use are perhaps occurring (Dorsey et al, 2010).

Atypical antipsychotics can relieve symptoms that arise in elderly patients with dementia:

- Anxiety and confusion

- Agitation with pacing, wandering, and restlessness
- Aggression (verbal and physical)
- Physical resistance and noncompliance with care
- Psychosis (hallucinations and delusions
- Depressive symptoms
- Sleep disturbances (day/night reversal, wandering behaviors)

Used appropriately and at low doses, anxiety, sleep disturbances, agitation, and aggression can be moderated without undue and adverse behavioral control. Some atypical antipsychotics are associated with weight gain, diabetes mellitus, and undue sedation (e.g., risperidone). Quetiapine (Seroquel) is associated with somewhat lower degrees of sedation, weight gain, and diabetes and therefore became preferred over risperidone. More recently, aripiprazole (Abilify) has been studied and is associated with even less sedation, little or no weight gain, presumably a lower propensity to diabetes, improvements in cognitive functioning, and a clinically significant antidepressant action. Used in low doses, these two newer agents confer anxiolytic effects with calming of agitated and aggressive behaviors; all with a reasonable degree of safety (Madhusoodanan and Shaw, 2008; Kohen et al, 2010).

In 2005, the FDA issued a public health advisory indicating a 1.7-fold risk of all-cause mortality from these drugs (all atypical antipsychotics) compared to placebo. Other researchers have failed to verify any increased risk of death. Indeed, while traditional antipsychotics likely carry some increased risk of cardiac mortality, this does not appear to extend to the atypical agents (Laredo et al, 2011; Mehta et al, 2011). Nevertheless, careful decision-making is warranted in the use of atypical antipsychotic medicines in this vulnerable population of persons.

An individualized, carefully monitored trial of these medications in anxious, aggressive, agitated elderly with dementia may result in improvements in quality of life both for the patient and for the caregivers. In these patients, benefits of medication may allow the patient to remain in a less structured and less confining environment than otherwise would be possible. Thus, the humanitarian benefits may outweigh any postulated increase risk associated with such use. These agents should be used with discretion and only as part of non-pharmacological, environmental, and behavioral interventions (Julien et al, 2011, page 651)

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FIGURE LEGENDS

Figure 3.1. Scores on the pediatric rating scale (ranging from 0 to 30) during 12 weeks of therapy with placebo, CBT alone, sertraline (Zoloft) alone, or a combination of CBT and sertraline. Scores higher than 13 are consistent with moderate levels of anxiety and a diagnosis of an anxiety disorder. Mean scores and standard errors are illustrated. From: Walkup, et al. (2008), Figure 2.

Figure 3.2. Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) scores during 12 weeks of acute treatment. Three groups were compared: (1) taking of a SSRI (no specific SSRI used) alone, (2) augmenting an SSRI either with a complete course of CBT (Plus CBT) or (3) instructions in CBT procedures (Plus instruction in CBT) delivered in the context of medication management (i.e., continuing treatment with an SSRI. Mean scores and confidence intervals are illustrated. From: Franklin, et al. (2011), Figure 2

Clinical Points to Remember

1. Man has sought medicinal relief from for millennia, from alcohols to barbiturates, benzodiazepines, benzodiazepine alternatives, to "tranquilizers", and even to atypical antipsychotics.

2. Consistently the major side effects associated with many anxiolytics include sedation, cognitive impairments, and psychomotor impairment.

3. The terms *Major Tranquiller* and *Minor Tranquilizer* are classic. Major Tranquilizer refers to sedating drugs used to treat schizophrenia (e.g., phenothiazines and haloperidol).

4. Proneness to future anxiety disorders may begin in the neonate; reductions in maternal affective disorders may reduce anxiety risk in the newborn.

5. Preschool anxiety disorders are common; pharmacological intervention is secondary to psychological interventions and should not be used with concomitant psychological therapy. Benzodiazepines (because of adverse learning effects) are not recommended; SSRIs are the pharmacological therapy of first choice.

6. Anxiety disorders in school-aged children and adolescents are common, disabling, and persistent into adulthood with lifelong implications. If medications are necessary, those with adverse effects on learning and memory should be avoided when possible.

7. In adult anxiety disorders, benzodiazepines remain widely used despite adverse addictive and cognitive side effects. SSRIs are widely chosen as initial agents, but efficacy is often incomplete. Therefore, knowledge of medications (e.g., anticonvulsants and atypical antipsychotics) for SSRI-resistant anxiety is essential.

8. In the elderly, anxiety disorders are common and often under-recognized and under-treated. Any agent that impairs mental functioning should be avoided. SSRI-type antidepressants may treat comorbid anxiety and depression.

9. Finally, in the elderly, certain atypical antipsychotic medications (e.g., risperidone and quetiapine) may calm anxious, aggressive, confused, and agitated patients. Weighing the positive effects in light of potential adverse reactions is essential. These drugs should not be used solely for behavioral calming.