 

Review Article

# Treating Anxiety with either Beta Blockers or Antiemetic Antimuscarinic Drugs: A Review

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## ABSTRACT

Beta adrenergic receptor antagonists and antiemetic muscarinic receptor antagonists are useful for mental health in primary care and family medicine settings, as they provide favorable risk/benefit profiles, and especially so relative to benzodiazepines. Beta blockers (e.g., propranolol) prescribed off-label have been known for decades to provide some, albeit limited, anxiolytic benefit for patients affected by social anxiety disorder (social phobia), including performance anxiety. Blockage of adrenaline's binding to cardiovascular beta adrenergic receptors inhibits tachycardia, reduces blood pressure, and thus diminishes palpitations in acute anxiety and panic. However, beta blockers are not effective against the psychic (CNS) symptoms, such as anxiousness, fear, and avoidance. Another approach involves antiemetic muscarinic receptor antagonists that are available by prescription (e.g., scopolamine) or over-the-counter (e.g., meclizine) for the treatment of non-cardiovascular symptoms that manifest in anxiety disorders. Antiemetic agents inhibit nausea, vomiting, sweating, and in some instances other psychic (CNS) symptoms. The symptoms affected by antimuscarinic agents represent the "inverse" of the symptoms of acute anxiety affected by beta blockers. Thus, anxiety disorders can be treated by alternative biochemical pathways, as well as by affecting alternative symptoms thereof. The results of human clinical studies are summarized for both classes of anxiolytic agents that display complementary pharmacologic approaches to a diverse array of symptoms.

**MeSH Headings/Keywords:** Anxiety, Panic, Anxiolytic, Beta Adrenergic, Muscarinic, Cholinergic, Antagonist, Scopolamine

## Introduction

The pharmaceutical marketplace in the Western World provides numerous medical treatments for anxiety disorders. Two classes of medications that have demonstrated some effectiveness and desirable risk/benefit profiles in the clinical literature are beta blockers and antiemetic antimuscarinic drugs. These agents have been widely used as monotherapies for a least half of a century around the globe.

They are appealing in large part due to historic safety profiles and because they do not exhibit the potential for chemical dependence or substance abuse. Therefore, these two classes of agents are not subject to the US Food & Drug Administration (FDA) and Drug Enforcement Agency (DEA) as Controlled Substances (i.e., "Scheduled" drugs). Furthermore, many antimuscarinic drug products are sold without prescriptions, such as over-the-counter (OTC) or in some foreign settings behind-the-counter with pharmacists' assistance.

Beta blockers and antiemetic antimuscarinic (anticholinergic) active pharmaceutical ingredients (APIs) are of particular interest for primary care physicians (PCPs), such as family practitioners, internists, and osteopaths, as well as physician assistants, nurse practitioners, and dentists. There is a need to provide drugs to their affected patients with some anxiolytic efficacy, yet without incurring unnecessary safety risks. In contrast, this is problematic with the alternative, more potent, and risk-laden options, such as benzodiazepines. The more potent drugs are more likely to be prescribed by psychiatrists or hospitalists. Many prescribers in primary care settings are reluctant to prescribe the more potent drugs (e.g., benzodiazepines) or are restricted from doing so. Thus, beta blockers and antimuscarinic agents help address this need, wherein safety is the paramount decision factor.

The biochemical pathways of the beta adrenergic receptor and muscarinic receptor gene families are appropriate anxiolytic targets for treating the symptoms of social anxiety disorder (social phobia) including performance anxiety (e.g., stage fright), as well as panic attack (PA), panic disorder (PD), agoraphobia, generalized anxiety disorder, and post-traumatic stress disorder (PTSD). These various anxiety Disorders are delineated within the Diagnostic and Statistical Manual of Mental Disorders (e.g., DSM-V). These molecular targets can be components of the central nervous system (CNS), the peripheral nervous system, and/or of target somatic tissues (e.g., cardiovascular and gastrointestinal tissues). The multiplicity of symptoms of anxiety disorders are under the complex regulation of different neurologic, neuroendocrine, and endocrine pathways.

Let us consider the multiplicity of symptoms that occur in an acute anxiety episode, of which a panic attack serves as the foremost and severe example. Perception of a "trigger" circumstance results in the autonomic release of epinephrine (adrenaline), as well as cortisol and norepinephrine. This in turn causes multiple effects consistent with a "fight-or-flight" response. Symptoms include tachycardia, palpitations (self perception of an elevated heart rate and/or of a strong heart beat), hypertension, hyperventilation with reduced blood $CO_2$ and altered pH, dyspnea, nausea, vomiting, sweating, anxiousness, fear, avoidance, trembling (tremors), headache, among others. Many of the somatic and/or psychic (CNS) symptoms of panic attack are shared in common with other acute anxiety episodes. Therefore, it follows that a treatment for an array of the symptoms of panic *per se* can also be effective against a broader list of anxiety disorders.

Some patients anticipate future episodes of panic or acute anxiety based upon his/her history of prior encounters with a known "trigger" circumstance. A trigger circumstance might

be public speaking or music performance, flying or driving, a crowd, decision making, an unfamiliar setting, among others. Treatments may be tailored to be either prophylactic or therapeutic in nature. Given the patients' anticipation of a trigger leading toward likely future symptoms, *p.r.n.* "as needed" drug treatments can begin either during or immediately prior to the time when symptoms would be expected to commence. Alternatively prophylatics could be administered continuously over weeks or years, or within hours of the anticipated triggers.

In aggregate anxiety disorders are extremely common, affecting nearly 40 million in the US. With regard to the subset experiencing the most severe episodes, the lifetime prevalence of PA is 28.3% of the adult US population [1]. The 12-month prevalence of panic disorder (PD) is estimated to be 2.7% of the adult US population [2], with 1.2% considered as "severe" [3]. More than half of affected adults (59.1% or ~ 3.8 million) are receiving treatment(s) [4]. Patients affected by PAs are often also affected by the co-morbid conditions of depression [5] as well as migraines and other forms of headaches [6,7].

The current standards-of-care for panic disorder are oral psychiatric prophylactic pharmaceuticals, including: (a) Selective serotonin reuptake inhibitors (SSRIs), which are considered as the first choice medicines for PD. Examples include paroxetine (Paxil®), sertraline (Zoloft®), and fluoxetine (Prozac®); (b) Benzodiazepines, such as alprazolam (Xanax®), clonazepam (Klonopin®), lorazepam (Ativan®), and diazepam (Valium®); and (c) Serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine (Cymbalta®) and venlafaxine (Effexor®). These oral therapies are taken daily for the prevention of panic attacks. Some of these drugs are FDA approved for the prophylaxis of PD, such as paroxetine, sertraline, alprazolam, and clonazepam. Other anxiety disorders are also treated in the same or a similar manner. For instance, social anxiety disorder, generalized anxiety disorder, agoraphobia, and PTSD are also treated using the same or similar oral daily pharmaceutical regimens [8].

The pharmaceutical standards-of-care in routine psychiatric care of panic and anxiety disorders involve two key aspects: (A) prophylaxis, rather than treatment of the symptoms per se; and (B) the medications are routinely given as daily oral "maintenance" medications for persistent use (i.e., chronic prophylaxis), rather than as occasional administration p.r.n. "as needed" at the time of episodes of symptoms (i.e., acute therapy).

Although oral benzodiazepines have been used as persistent daily medications for the prophylaxis of panic and acute anxiety, they are not reasonable candidates for a "fast-acting" p.r.n. therapy approach. Benzodiazepines are often mistakenly considered to be "fast-acting", although multiple clinical reports indicate otherwise. Zamorski and Albucher stated, "Benzodiazepines should not be used on an as-needed basis for panic disorder. None of the oral benzodiazepines works quickly enough to affect any but the most prolonged panic attacks [9]." Altamura, et al. stated recently, "…it would be desirable for the development of new anxiolytic drug(s) that are more selective, fast acting and free from the unwanted effects associated with the traditional benzodiazepines as tolerance or dependence [10]." Altamura and coworkers also stated regarding benzodiazepines as a class of anxiolytic drugs, "Only lorazepam is currently available in a form suitable for sublingual administration, which was developed in the hope that, by bypassing the gut, a more rapid onset could be achieved similar to that with intramuscular administration. However Greenblatt et al., [11] found that the sublingual formulation was absorbed at a rate that did not differ significantly from that of regular oral administration of the standard tablets or even from that of sublingual administration of the standard oral tablets." Thus, benzodiazepines are not suitable APIs for rapid treatment of symptoms of panic attacks or acute anxiety episodes, even when delivered sublingually (mucosally). When "time is of the essence" for therapy, benzodiazepines are inadequate, regardless of the oral or sublingual routes of administration. Perhaps the perception of benzodiazepines' fast-action is due to comparison with SSRIs, which require a very slow dose-escalation approach over weeks of time to produce a beneficial effect. In that context benzodiazepines are faster than SSRIs. But, in spite of FDA approvals for p.r.n. use of certain benzodiazepines and their broad availability, there still remains a need for fast-acting p.r.n. anxiolytics. In fact, an academic psychiatrist characterized this need to the author as "…the Holy Grail of modern psychiatry."

Benzodiazepine and SSRI drugs can produce disabling psychic and somatic side effects, such as sedation, lethargy, chemical dependence, tolerance, impaired cognition, and sexual dysfunction. As a result of these negative side effects and some potential for abuse, benzodiazepines are classified by the FDA as Schedule 4 (IV) Controlled Substances. Many physicians and other prescribers are reluctant to prescribe or are restricted from prescribing benzodiazepines. Therefore, beta blockers or antiemetic agents that are generally perceived as historically safe or safer than benzodiazepines are often preferable. This is especially true in the primary care and family practice disciplines. Sedation and lethargy are often problems for many of the oral daily anxiolytic therapies, such as benzodiazepines. It is not uncommon to note a "zombie-like" state in patients taking benzodiazepines. By contrast, beta blockers are non-addicting and non-sedating. And, the antimuscarinic agents are non-addicting, and are non-sedating or minimally sedating at appropriate antiemetic doses. However, high doses of some antiemetics can produce sedation.

**Beta Blockers**: Beta adrenergic receptor antagonists are prescribed "off label" (i.e., without FDA approval) for anxiety disorders, and most notably for performance anxiety and social phobia. Beta adrenergic receptor antagonist agents may be selected from a large group of APIs consisting of propranolol, atenolol, alprenolol, acebutolol, betaxolol, bisoprolol, bucindolol, celiprolol, nadolol, sotalol, esmolol, carteolol, carvedilol, mepindolol, nebivolol, oxprenolol, penbutolol, pindolol, landiolol, metoprolol, timolol, labetolol, among others. For convenient recall by prescribers the nomenclature for all beta blockers contains an "LOL" suffix (and not to be confused with the abbreviation for "laughing out loud").

Propranolol is the most thoroughly studied and reported in the literature of the beta blockers, having been discovered by Sir James Black in 1958. It serves as the prototype for this class of drugs, having also been the most prescribed medicine in the world at one juncture. Propranol is a beta adrenergic

receptor antagonist that affects the autonomic nervous system and reduces cardiovascular symptoms (e.g., tachycardia and hypertension) resulting from epinephrine in the circulation. Beta blockers interfere with receptor binding by catecholamines, epinephrine and norepinephrine, of which epinephrine is the principal catecholamine affecting the cardiovascular symptoms. Propranolol is a lipophilic beta blocker that readily crosses the blood-brain barrier. Therefore, it can affect both somatic and CNS target tissues.

Propranolol is routinely delivered orally. Propranolol in Inderal® is available in oral doses ranging from 10 to 80 mg per dose for the treatment of hypertension. Multiple doses per day may be permitted. This drug can also be absorbed mucosally, as demonstrated by sublingual delivery [12], and its bioavailability is higher when absorbed by this route rather than orally [13,14]. Propranolol has been delivered sublingually at 10 and 40 mg per dose [12,13], although this can produce mouth paresthesia, an undesirable effect. Also, propranolol has been delivered by rectal administration in mammals [15]. It does not demonstrate chemical dependence or sedation that are common side effects of many psychiatric medications.

Propranolol is prescribed for the treatment of various cardiovascular indications with FDA approval, most notably hypertension, arrhythmia, angina, as well as prophylaxis of migraines. However, there is evidence that it can have some benefit with regard to a subset of the symptoms of panic and anxiety disorders. The drug's anxiolytic potential was recognized as early as 1966, "Emotions are expressed through the autonomic nervous system, and anxiety states are associated with increased secretion of catecholamines. Propranolol may therefore have a place in the treatment of anxiety, especially when the symptoms are related to the cardiovascular system [16]." This prescient comment five decades ago was subsequently validated by clinical studies with regard to both aspects: (a) propranolol and other beta blockers have been used "off label" in the USA for the near-term prophylaxis of performance anxiety; and (b) the pharmacologic benefits of propranolol and other beta blockers are restricted to the cardiovascular system's effects per se. The evidence is provided below. The beneficial anxiolytic effects are limited to blocking the pharmacologic effects of catecholamines upon the cardiovascular system without addressing the psychic (CNS) symptoms or other somatic symptoms of acute anxiety and panic, with the possible exception of tremors.

(Table 1) summarizes the relevant evidence from clinical investigations in the literature regarding beta blockers used to treat anxiety conditions. Daily oral propranolol has been demonstrated in one prophylactic study to suppress panic attacks in subjects diagnosed with panic disorder and agoraphobia [17]. Tyrer and Lader demonstrated some effectiveness of oral propranolol in treating somatic anxiety symptoms, but not psychic (mental) anxiety [18,19]. Another daily oral prophylactic study compared propranolol (3 x 80 mg/day) to oxprenolol (3 x 80 mg/day) and revealed that both beta blockers reduced symptoms of anxiety at one or two weeks duration [20]. Both treatments reduced heart rate; propranolol by ~ 21 - 32 bpm and oxprenolol by ~ 16 - 23 bpm. However, propranolol was more effective at reducing palpitations when assessed on day 7 compared to oxprenolol. Another study demonstrated that a single dose of 40 mg of oxprenolol prior to speaking to an audience suppressed tachycardia in performance anxiety [21]. In contrast, in another clinical study daily oral propranolol was not effective at treating panic disorder and agoraphobia with panic attacks [22].

**Table 1:** Clinical Evidence for Beta Blockers as Anxiolytics.

| DRUGS | CONDITIONS | REFERENCES |
|---|---|---|
| Propranolol | Anxiety | 18-20 |
| " | Panic | 17 |
| " | Performance anxiety | 53 |
| " | Test-taking anxiety | 23-24 |
| " | Cognitive flexibility | 26, 43-44 |
| " | PTSD | 36-40 |
| " | Aggression | 74-75 |
| " | Migraine | 65-70 |
| " | Cocaine withdrawal | 59-60 |
| " | TSST-induced anxiety | 25-28 |
| " | $CO_2$-induced panic | 35 |
| Atenolol | Performance anxiety | 45 |
| " | Alcohol withdrawal | 54-56 |
| Pindolol | Performance anxiety | 51 |
| " | Alcohol withdrawal | 57 |
| Timolol | Alcohol withdrawal | 58 |
| " | Migraine | 72-73 |
| Nadolol | Performance anxiety | 48-49 |
| Betaxolol | Anxiety & panic | 52 |
| Oxprenolol | Anxiety | 20 |
| " | Performance anxiety | 21 |

There is some evidence suggesting that propranolol might be beneficial in academic test-taking among normal and anxiety-prone students. Examination performance might be increased by pretreatment with this beta blocker [23, 24].

To assess the clinical efficacy of an anxiolytic drug, trials can be performed either "in life" or in a laboratory setting intended to induce anxiety. One established clinical trial design to provoke anxiety is the Trier Social Stress Test (TSST). This method is used in a clinic and involves subjecting an individual to public speaking and mathematics questions as stressors.

The TSST method has been used to study the effects of oral propranolol in volunteer subjects [25-28]. The assessments of psychic anxiety can be assessed by the State-Trait Anxiety Inventory (STAI) or other similar tools [29,30]. The somatic and psychic effects of oral propranolol were tested using the TSST method in healthy adult volunteers. Propranolol (40 mg) one hour prior to TSST significantly reduced heart rate, reduced systolic blood pressure, and enhanced cognitive flexibility during stress. In another study propranolol (80 mg) one hour prior to TSST significantly reduced heart rate, but paradoxically increased salivary cortisol, and did not significantly affect BP or subjective stress [25]. But, in another TSST study daily oral propranolol (80 mg) did not affect the salivary cortisol response [27].

An alternative clinical trial design involves the intentional chemical provocation of a panic attack in a clinic. Several methods of provocation of PA have been reported, wherein

**Table 2:** Clinical Evidence for Antimuscarinic Agents as Anxiolytics.

| DRUGS | CONDITIONS | REFERENCES |
|---|---|---|
| Scopolamine | Depression | 83, 91-94 |
| " | Manias | 102 |
| " | Anxiety | 93 |
| Hydroxyzine | Anxiety | 84-86 |
| " | Panic | 87-88 |
| Promethazine | Anxiety | 90 |
| Orphenadrine | Depression | 99-100 |
| Tofenacin | Depression | 99, 101 |

a physician intentionally stimulates a physiologic response by $CO_2$ inhalation [31], sodium lactate infusion [32,33], or cholecystokinin tetrapeptide (CCK-4) injection [32,34]. These chemical exposures are used as potent tools to design controlled studies with predictable levels of PA episodes. In a study with healthy volunteer subjects using carbon dioxide inhalation to provoke panic and anxiety, propranolol significantly decreased heart rate, a cardiovascular somatic symptom, but did not provide psychic anxiolytic benefit [35].

Propranolol has also been investigated in patients suffering from severe posttraumatic stress disorder (PTSD). Two clinical studies of this beta blocker have shown possible benefits in the early-stage interventional prevention and subsequent therapy of PTSD [36,37]. Subsequent reports have also echoed that propranolol might be effective for this condition [38-40], although other reports dispute this conclusion [41,42].

When considered in aggregate these clinical studies of propranolol, as the well known prototypical beta blocker, provide convincing evidence that the drug can exert somatic (i.e., peripheral) effects on the cardiovascular system in the context of panic and anxiety disorders. With regard to affecting the psychic (CNS) symptoms, the results have been negative, inconsistent, or inconclusive. That being said, there is some limited evidence that propranolol can exert some psychic (CNS) benefits in clinical stress trials. In a pair of clinical studies, propranolol (a central and peripheral beta-blocker) significantly enhanced problem solving during stress, whereas nadolol (peripheral only beta-blocker) and lorezapam (benzodiazepine) did not [43, 44]. Thus, propranolol enhanced cognitive flexibility ("creativity") during stress. It remains unclear whether propranolol alone can appreciably reduce psychic effects. In aggregate the clinical evidence does not support a benefit regarding psychic (CNS) anxiety symptoms.

Numerous alternative beta blockers are available in lieu of propranolol. Notable among these is the common drug, atenolol, that is available in oral solid dose forms ranging from 25 to 100 mg for the treatment of hypertension. Multiple doses per day may be permitted. It has been used to suppress stage fright in performers when administered orally in advance [45]. Atenolol is a beta-1 selective peripheral-acting agent without CNS effects, which should reduce the risk for asthmatic subjects [46]. Thus, atenolol might be preferred over the nonselective beta blockers for patients affected by asthma or COPD [47]. Oral atenolol at 50 - 200 mg doses suppressed heart rate by ~ 23 - 24 beats per minute (bpm) vs. ~ 10 bpm on placebo [46]. Also, atenolol has been delivered by a mucosal route in mammals [15].

Another beta blocker is nadolol, which is non-selective and with a preference for beta-1 receptors. It does not pass through the blood-brain barrier. In a clinical trial with musicians, nadolol reduced pulse rate and improved one aspect of performance related to tremor [48]. A similar result was obtained for nadolol in students' singing performance [49]. In spite of being non-selective, nadolol might ironically benefit the pulmonary function in asthma patients based upon the appropriate dosage, an anti-intuitive result [50].

An alternative beta blocker is pindolol, a non-selective agent, which can enhance the effects of co-administered antidepressants and has some 5-HT antagonist property. Pindolol reduced symptoms of performance anxiety in musicians [51].

Another example is betaxolol that can also cross the blood-brain barrier. Daily oral betaxalol was delivered at 5 - 40 mg per day in the treatment of generalized anxiety disorder and other anxiety-related conditions. Anxiety and panic attacks were reduced within several days [52]. This anxiolytic benefit is prophylactic, as the effects are observed in days, rather than in minutes.

In view of the clinical studies and off-label use of various beta blockers, psychiatrists are aware that beta blockers can provide some symptomatic relief with regard to performance anxiety [53]. However, beta blockers alone do not sufficiently address the aggregate symptoms of panic and acute anxiety episodes, and especially the psychic symptoms thereof (e.g., fear, avoidance, and anxiousness).

Beta blockers also exhibit some benefit with regard to alcohol and drug abuse. The abuse of alcohol, prescription drugs, and illegal drugs (e.g., opioids, opiates, and cocaine) are major mental health care concerns. The repetitive abuse of these chemicals can produce physiologic dependence, tolerance, addiction, and neurologic damage. The symptoms of sudden withdrawal depend upon the abused substance, the impairment of neurological and neuroendocrine pathways, as well as somatic organ impairment. The withdrawal from addictive substances produces an array of symptoms, many of which overlap with the symptoms of panic and acute anxiety episodes. Delirium tremens (DTs) occur in some alcoholics upon abrupt cessation of drinking. The symptoms of alcohol-related DTs are very similar to those of panic attacks, and are in part related to beta adrenergic effects. The DTs can have serious and even life-threatening consequences. The standards-of-care for DTs are oral benzodiazepines. Withdrawal from opioid and/or opiate addiction is physiologically distinct from alcohol withdrawal.

With regard to beta blockers in substance abuse, atenolol has been shown in placebo-controlled trials to be beneficial in alcohol withdrawal [54-56]. Pindolol has been used to treat alcohol withdrawal [57]. Timolol had a minimal effect on a subset of symptoms of patients experiencing alcohol withdrawal [58].With regard to cocaine abuse, propranolol has been used to treat withdrawal and overdoses [59, 60]. Note that propranolol has also been shown to suppress tremors [61], consistent with one of the perceived benefits of beta blockers in performance anxiety in musicians (above).

Migraine is a co-morbid condition in approximately two-thirds of patients suffering from panic disorder [6,62]. The prevalence of migraine in the USA according to the American Migraine Prevalence and Prevention (AMPP) study is 11.7% and probable migraine is 4.5%, for a combined total of 16.2% [63]. The rate is higher in females than in males. According to Smitherman and coworkers, "The first-line migraine prophylactics are not indicated for PD, and the selective serotonin re-uptake inhibitors used to treat PD are not efficacious for migraine; thus, separate agents are often required to address each condition [6]." Furthermore, according to Marazziti and coworkers, "…the comorbidity of headache with panic disorder renders this condition more severe and possibly responsive to different treatments compared to panic disorder alone [64]."

It is feasible that a beta blocker alone may provide therapeutic benefit for both conditions, panic and migraine. Beta-adrenergic receptor antagonists are considered to be effective prophylactics for chronic or episodic migraine [65-70]. Although one study reported no benefit from propranolol for treatment of acute symptoms [71], there is some, albeit limited, evidence that beta adrenergic receptor antagonists, especially when delivered mucosally, can also have benefit in the therapy of acute migraine [72,73].

Beta blockers may be effective as a treatment for aggression. Systemic adrenaline can produce excited, anxious, and aggressive behavior in some individuals. Propranolol has been shown to have a therapeutic effect with regard to aggressive behavior [74,75].

Although psychiatrists (and some other physicians) are aware of off-label use of beta blockers as prophylactics for performance anxiety (e.g., stage fright during musical performances), the current pharmaceutical standard-of-care for anxiety disorders does not routinely include the use of beta blockers. But, beta adrenergic receptor antagonists can provide limited benefit, such as the suppression of cardiovascular symptoms - tachycardia, palpitations, and increased blood pressure, which are symptoms of acute anxiety episodes and panic. That being stated, Zamorski and Albucher concluded, "Beta blockers, once widely touted as effective antipanic medications, have proven disappointing as monotherapy in subsequent placebo-controlled trials." The multiplicity, severity, and short duration of symptoms in a panic attack make it a difficult disorder to treat by p.r.n. therapies.

**Muscarinic Receptor Antagonists:** Scopolamine is the prototypical antiemetic antimuscarinic agent. It is a plant-derived natural product derived from the Solanaceae "nightshade" family of plants (e.g., jimson weed), and is commonly used for the treatment of motion sickness, nausea, and vomiting. It is a potent nonselective muscarinic receptor antagonist that can inhibit all five human receptor subtypes with ~ 0.34 - 5.3 nM Ki values [76]. It is lipophilic and crosses the blood-brain barrier to exert psychic parasympathetic (CNS) pharmacologic effects.

Scopolamine is sold by prescription in the USA as a transdermal patch (Transderm Scop®) [77]. However, scopolamine is available without a prescription in many foreign markets, where it can be purchased OTC or behind-the-counter with pharmacist's assistance. For instance, in Australia it is an oral OTC product with a recommended adult dose of 0.3 or 0.6 mg, and a maximum daily dose of 1.2 mg [78]. Scopolamine can also be absorbed mucosally, as demonstrated by sublingual delivery [79,80]. It has been delivered sublingually at 0.15 mg/dose [79], intranasally at 0.4 mg [81,82], orally at 0.4 - 1.0 mg/dose [80,83], and transdermally (Transderm Scop®) at 1.5 mg/dose over 3 days as antiemetic treatments or prophylactics. Oral delivery, unlike mucosal or transdermal delivery, involves first-pass hepatic metabolism of scopolamine, thus restricting its bioavailability.

Antiemetic muscarinic receptor antagonist agents can be selected from a large group beyond scopolamine, examples of which include diphenhydramine, meclizine, buclizine, cyclizine, hydroxyzine, pirenzepine, benztropine (benzatropine), atropine, hyoscyamine, butylscopolamine, methylscopolamine, doxylamine, promethazine, trihexyphenidyl, orphenadrine and its metabolite tofenacine. Depending on the choice of country, OTC or "behind-the-counter" antiemetic antimuscarinic agents include diphenhydramine, orphenadrine, doxylamine, meclizine, buclizine, cyclizine, and scopolamine. This further underscores the perception by regulatory agencies of the safety of antimuscarinic agents. Dryness of the mouth is a common side effect of antiemetic agents.

Structurally-related derivatives of scopolamine are alternative antimuscarinic APIs, such as butylscopolamine, methylscopolamine, atropine, hyoscyamine (the levo isomer of atropine), and benztropine (benzatropine). For instance, peripherally-acting butylscopolamine (scopolamine butylbromide) is used for the treatment of abdominal spasms. The butylbromide modification prevents the API from crossing the blood-brain barrier. However, direct pharmacologic action by the antimuscarinic agent upon the CNS might be preferable, if not necessary, for mediating psychic benefits in anxiety.

In addition to the scopolamine "family" of APIs, there are other closely-related families of APIs exhibiting antimuscarinic activities. In some cases the APIs also exhibit antihistamine properties. Examples of other "families" of antiemetic antimuscarinic agents include: (a) Ethanolamines: diphenhydramine (Benadryl®), doxylamine (Unisom® or Nyquil®), orphenadrine (an OTC in Canada) and its metabolite tofenacine; and (b) Piperazines: meclizine (Dramamine® Less Drowsy Formulation or Bonine®), buclizine, cyclizine, hydroxyzine (Atarax® or Vistaril®), and pirenzepine. Furthermore, other types of antiemetic antimuscarinic agents are available, such as promethazine (Phenergan®) and trihexyphenidyl.

(Table 2) summarizes the relevant evidence from clinical investigations in the literature regarding antimuscarinic agents used to treat anxiety conditions. Hydroxyzine is an FDA-approved prescription medicine for the treatment of anxiety [84]. The package insert for Atarax® (Roerig) states it is indicated "for symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested." As a first-generation antihistamine this drug entered the healthcare marketplace in the mid-1950's. It displays broad receptor binding, affecting histamine, muscarinic, and 5-HT receptors. Placebo-controlled studies with a total daily dose of 50 mg have revealed anxiolytic benefit following weeks or months of treatment in generalized

anxiety disorder [84-86]. This "old" drug is no longer among the frontline choices for anxiety, having been superceded by benzodiazepines and subsequently SSRIs and SNRIs. However, it has at least two beneficial properties -- an effect can be perceived faster than many other oral anxiolytics, and like other antimuscarinic agents it has a desirable risk/benefit profile (i.e., doesn't produce dependency). In addition to treating generalized anxiety disorder, a few case reports suggests it might be beneficial in treating panic disorder [87,88].

Promethazine is another antimuscarinic agent with antihistamine and CNS activities. Oral promethazine at 25 mg/dose reaches a peak serum level ($C_{max}$) in 2-3 hours, which is relatively slow for an oral drug, and can result in drowsiness within a similar time window [89]. As a premedication prior to surgery, it produced an anxiolytic effect that was substantially greater than placebo [90].

Although depression *per se* is not the focus of this review, selected antimuscarinic agents can display psychic (CNS) pharmacologic effects on mood, such as depression (e.g., major depressive disorder). Scopolamine can exhibit an antidepressant effect when administered intramuscularly [91], intravenously [92-94], or orally [83]. With regard to patients treated with i.v. infusions of 4 ug/Kg (e.g., 0.28 mg/70 Kg), "Significant clinical responses were observed in the evaluation after the first scopolamine administration, 3 to 4 days after the first treatment." And, "…those patients who observed an improvement in their depression severity generally reported relief from their depressive symptoms on the first morning after scopolamine infusion (i.e., within 24 hours of drug exposure). In contrast, no improvement in mood was evident within 150 minutes of scopolamine infusion based upon the POMS" (i.e., Profile of Mood States) [95]. Although i.v. administration at 4ug/Kg can affect depression, many patients receiving this treatment regime also experienced sedation. In addition, they experienced dry mouth, blurred vision, and/or lightheadedness.

The efficacy and side effects of a drug are dependent upon the dose delivered and the route of administration. It should be noted that the pharmacokinetic magnitude of effect and the time to reach an effect of a "typical" API is very likely to exhibit a range from intravenous > intramuscular or mucosal > oral >> transdermal. This pattern is in fact the case for scopolamine in humans. As an example thereof, intramuscular injection of 0.5 mg of scopolamine displayed only 57% of the absolute bioavailability relative to i.v. infusion of the same dose, and is subject to some delay [96]. Thus, an i.v. antidepressant dose of 0.28 mg/70 Kg of scopolamine is very likely to have an immediate and more profound physiologic effect relative to the same dose via other routes of delivery, because there are no membrane and tissue barriers to entry into the circulation when injected intravenously. By contrast intranasal (mucosal) dosing of 0.4 mg results in a $C_{max}$ (i.e., the peak level in the blood) after 22 minutes [82]. Oral dosage forms of 0.6 mg displayed a peak plasma level at ~ 50 minutes [97]. And, the 1.5 mg transdermal patch produces a $C_{max}$ of ~ 8 hours [98]. Thus, the timing to reach peak blood levels of scopolamine by various routes of administration is or should approximate this progression: i.v. at ~ 0 min. > intranasal (mucosal) at 22+ min. > oral at ~ 50 min. >> transdermal at ~ 8 hours. In general, the perception of pharmacologic effects can precede the zenith of plasma levels, except for rapid intravenous administration wherein pharmacologic effects might be concurrent or delayed slightly.

The antidepressant dose via the i.v. route (4 ug/Kg) is likely to be above the blood levels attained during routine antiemetic dosing (e.g. transdermal patches or oral dose forms), wherein sedation would be considered a significant and undesirable side effect. For comparison, sedation is generally considered in the literature to occur at 1.2 mg or higher by the oral route. Scopolamine has been used as a safe pre-sedative, for instance in pregnant women prior to delivery.

In addition to scopolamine, two other muscarinic receptor antagonists, orphenadrine and its major metabolite, tofenacine, have also been reported to exhibit an antidepressant effect [99-101]. Orphenadrine is beneficial in treating multiple symptoms of Parkinsonism. Orphenadrine administered orally (300 mg/day) for three weeks in patients afflicted by Parkinsonism was very effective at blocking depression relative to placebo [100]. Tofenacine at 120 – 240 mg/day for six weeks was effective in treating neurotic depression, endogenous depression, mixed depression, and phobic anxiety diagnoses and within two weeks of initiation of therapy [101].

Although not common knowledge among physicians at present, there is some historic evidence that scopolamine can exert anxiolytic effect(s). Scopolamine was described a century ago to have a "*calming effect*" when injected hypodermically into patients afflicted by various psychiatric disorders (e.g., manias) at doses of 0.2 - 1.0 mg [102]. Coincidentally, these doses are still relevant in clinical use to this day. This 1906 publication mentioned, "…the calming effect of the medicament…The action of scopolamine shows itself rapid in maniacal excitement and in acute hallucinatory delirium. The patients become calm gradually, and fall asleep if the dose is somewhat larger."

A genetic study of the human M2 muscarinic receptor gene (*CHRM2)* has revealed an association between specific genetic polymorphisms and the risk of depression in major depressive syndrome [103]. Consistent with these pharmacologic and genetic findings in humans are laboratory studies with rodent models for antidepressant activity. Both pharmacologic and gene knock-out approaches in mice revealed that the antidepressant-like effects of scopolamine are mediated via the M1 and/or M2 receptors, but not the M3, M4, and M5 receptors [76]. Thus, the human M2 (and/or M1) receptor-linked second messenger signaling pathways in the CNS are likely to affect mood and mood disorders (e.g., depression).

Alcohol dependence is comorbid with depression, and has been genetically linked to the same human *CHRM2* gene encoding the M2 muscarinic receptor. Scopolamine has an M1 receptor preference over M2, but it can also bind the M2 receptor [76,103]. Thus, there is a convergence between the genetic and the pharmacologic studies in both humans and laboratory mice, thereby providing a suggested rationale for the use of scopolamine in treating alcohol addiction and/or withdrawal. These findings might also apply to other antiemetic antimuscarinic agents beyond scopolamine.

Scopolamine has also been shown to reduce aggressive behavior in nonhuman primates under certain environmental

circumstances [104]. It is not yet clear whether this is also true in humans. But, it can be argued that an anxiolytic calming effect might similarly reduce aggression in some humans, which is perhaps suggested by its historic effect in treating "maniacal excitement" [102].

**The Future – Beyond Monotherapy:** The monotherapies mentioned above provide some, albeit limited, pharmacologic efficacy for anxiety disorders, yet while being historically safe approaches to therapy and/or prophylaxis in mental health. Reaching beyond current monotherapies, another approach is combination therapies with two or more APIs. Combination drugs can be sold legally to patients, albeit subject to various alternative regulatory oversight processes.

Within the USA combination drug products may be FDA approved for specific medical indications through the FDA's drug approval processes that can result in either approved prescription (Rx) drugs or approved OTC drugs. Alternatively, compounding pharmacies may formulate multiple APIs into a compounded pharmaceutical product via either the 503A or 503B regulatory pathways. But, key parameters must be met for compounded products. For instance, several of the restrictions include: (a) Each of the APIs must have been included in at least one FDA-approved medication; (b) The compounded product must not be a copy of an FDA-approved combination drug; and (c) The compounded products are subject to USP 795 or USP 797 standards and procedures during compounding or "outsource" facility manufacturing, respectively. These compounded products are sold by prescription only as "unapproved" products, although subject to state boards of pharmacy and FDA regulations.

In view of the historic scientific and clinical literature mentioned above on beta blockers or antiemetic drugs as monotherapies for anxiety disorders, the author recognized both a need in the pharmaceutical marketplace and an opportunity to augment the limited cardiovascular benefits of a beta blocker with another type of API to produce a superior anxiolytic therapy for p.r.n. administration. It would be advantageous for the augmenting second agent: (a) to address other symptoms; (b) to exert some psychic (CNS) pharmacologic benefits; (c) to have a rapid effect; and (d) to not be a Controlled Substance. Thus, the augmenting second API could not be an opiate, opioid, benzodiazepine, SSRI, or cannabinoid. This led the author to an innovative conclusion; a combination of a beta blocker plus an antiemetic antimuscarinic agent should be of substantial clinical benefit and reaching beyond the pharmacologic benefits of either class of drugs acting alone as monotherapies.

Searches of the literature did not reveal any precedents for this dual drug combination therapy approach using these two classes of agents (i.e., beta blocker plus antimuscarinic agent) in any medical indication in mental health or psychiatry. Secondarily, searches did not reveal any record of both classes of APIs being formulated together into a single drug formulation. Thus, this dual drug approach was novel with regard to both aspects, even though both classes of drugs have been in commercial use for over five decades.

That being said, one relevant article addressed the coincidental co-administration of a beta blocker with an antimuscarinic agent in healthy volunteers when exposed to heat within a sauna [105]. The beta blocker was selected because heat induces cardiovascular stress, especially elevated heart rate. Scopolamine was selected as it is known to reduce sweating. The cardiovascular effects of oral atenolol (50 mg), oral scopolamine (0.3 mg), and coincident administration of both drugs were monitored before, during, and after heat stress. The coincident administration of both drugs revealed essentially the same cardiovascular effects as atenolol alone (i.e., reduced heart rate and blood pressure), and either at baseline prior to heat exposure or during it. The relevant antiemetic oral dose of scopolamine alone or as an adjunct to atenolol displayed essentially no effect with regard to the cardiovascular symptoms, although a slight tachycardia occurred with scopolamine relative to placebo. Overall, the cardiovascular effects (i.e., reduced heart rate and systolic BP) were due to atenolol. Thus, scopolamine co-adminstration did not abrogate the cardiovascular effects of the beta blocker. The potential for any psychiatric and/or psychic (CNS) effects of scopolamine and/or atenolol were not envisioned or addressed by this study.

In view of these results [105] and given that episodes of acute anxiety and panic are driven physiologically in part by increased epinephrine's effects on the cardiovascular system, it is appropriate to include within a combination therapy a beta blocker to address the cardiovascular symptoms *per se* of anxiety disorders. Based upon the literature an antimuscarinic agent alone would not be anticipated to be of benefit for the cardiovascular symptoms of these psychiatric conditions. Coincidentally, the antimuscarinic agent atropine is known to produce tachycardia, and scopolamine to a lesser extent. Tachycardia is antithetical to the desired outcome.

It should be emphasized that palpitations (resulting from elevated heart rate and/or blood pressure) are considered to be the predominant symptom that patients are aware of during panic attacks and acute anxiety episodes. The beta blocker, within a dual drug product, should address this primary (major) symptom of panic and acute anxiety episodes.

Recently the author has developed novel pharmaceutical formulations to address the augmentation of a beta blocker's effects on the cardiovascular symptoms with an antiemetic antimuscarinic agent's effects on non-cardiovascular symptoms (unpublished results). This new dual drug approach holds substantial promise to address *p.r.n.* all or most of the symptoms of acute anxiety episodes or panic, neither of which is addressed by a beta blocker alone or an antiemetic antimuscarinic agent alone. The dual drug compositions provide a complementary broad coverage of the symptoms of acute anxiety: the beta blocker provides benefits with regard to cardiovascular symptoms (e.g., palpitations, heart rate, and BP); and, the antimuscarinic agent provides benefits with regard to non-cardiovascular symptoms (e.g., nausea, vomiting, sweating, anxiousness, avoidance, fear, etc.).

It should be noted that augmentation of a beta blocker with an antimuscarinic agent, wherein the latter only affects a subset of the common symptoms of acute anxiety (i.e., nausea, vomiting, sweating, and/or motion sickness) *per se* would provide anxiolytic superiority over a beta blocker alone or an antiemetic agent alone. In other words, even without affecting psychic symptoms (e.g., anxiousness, fear, avoidance, etc.), the dual drug approach

has substantial merits for treatments of the symptoms of anxiety disorders.

This novel dual drug approach may also be of value as a supportive *p.r.n.* therapy during cognitive behavioral therapy (CBT) or other forms of counseling for anxiety and panic. The pharmaceutical compositions may provide anxiolytic benefit without cognitive impairment while learning or reinforcing desirable behaviors. The dual drug therapies may also be used when the patients experience acute anxiety episodes or panic between sessions of CBT or other forms of counselling. The calming effect may improve voluntary and involuntary motor control, task performance, cognition, memory, and may reduce fear, avoidance, and anxiousness in patients. Furthermore, having a convenient fast-acting *p.r.n.* dual drug medication in one's pocket or purse might coincidentally serve as a palliative "security blanket" to enable greater functionality, regardless of whether the patient self-administers the medication for symptoms of acute anxiety or panic [88].

At this juncture, the novel dual drug approach appears promising for rapid *p.r.n.* treatment of acute anxiety episodes and panic. This therapeutic option may be especially appealing in primary care settings, such as family medicine, wherein a favorable risk/benefit ratio is highly significant in a prescriber's decision-making process when considering therapeutic options.

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## Disclosure

The beta blocker plus antimuscarinic drug combination therapy approach is patent pending in the USA and internationally and may be subject to the US Trademark PanX™. 

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