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Anxiolytic benefits of compounded Atenolol–Scopolamine in eight patients in psychiatry

Ashley B. Benjamin[a,*], Thomas P. Dooley[b]

[a] 4935 Via Camino, Newbury Park, CA 91320 USA
[b] Trends in Pharma Development LLC, 7100 Cabin Lane, Pinson, AL 35126, USA

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ABSTRACT

There is an unmet medical need for fast-acting, effective, non-dependent and non-addicting anxiolytic treatments, in lieu of benzodiazepines. Compounded tablets of PanX® Atenolol–Scopolamine HBr were administered orally in eight patients with complex diagnoses receiving residential psychiatric care for acute anxiety and/or other conditions. Three of the eight patients were being treated for substance abuse. The primary endpoint was a reduction in the severity of "State" anxiety symptoms using the Beck Anxiety Instrument (BAI-S), prior to drug administration and one hour and/or approximately four hours after oral administration. Six of the eight patients were responders with a perceived calming effect and substantial reductions in their BAI-S scores. The mean of the BAI-S scores for all eight patients, including two deemed as non-responders, were 15.9 at baseline pre-treatment, 8.5 at 1 h post-treatment, and 4.1 at approximately 4 h. The mean of the heart rate was reduced from 93.6 bpm pre-treatment to 77.0 bpm at 1 h post-treatment and 79.7 bpm at 4–5 h. The mean of the blood pressure decreased by 10.1 mmHg systolic and 5.3 mmHg diastolic at 1 h post-treatment and even greater at 4–5 h. The reductions in heart rate and blood pressure are consistent with the effects of the beta blocker Atenolol. The drug combination was well tolerated in all patients with minor side effects in some, i.e., dry mouth and mild sleepiness (mild sedation). The beneficial reduction in anxiety symptoms was perceived within 15–60 min and persisted for up to 8 h.

1. Introduction

Anxiety disorders are extremely common. The 12-month prevalence of any anxiety disorder in the US is 18.1%. Therefore, approximately 45.5 million adults are affected by anxiety disorders in the US. The FDA-approved standards-of-care prophylactics and/or treatments for anxiety disorders are selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, serotonin-norepinephrine reuptake inhibitors (SNRIs), and other agents (e.g., Buspirone and the antihistamine Hydroxyzine). In spite of the availability of approved anxiolytic medications, there remains an unmet medical need for fast-acting and effective anti-anxiety treatments that do not produce dependence or addiction.

A patented new class of anxiolytic medications has been developed to address this unmet medical need without using dependent/addictive active ingredients. The patented PanX® medications consist of a beta blocker to inhibit the sympathetic symptoms of anxiety disorders in combination with an antiemetic antimuscarinic (motion sickness) agent to inhibit the parasympathetic symptoms [1]. PanX® drugs are intended as alternatives to benzodiazepines (e.g., Alprazolam, Clonazepam), which pose significant risks of side effects such as dependence (i.e., adverse withdrawal reactions), memory impairment, addiction, misuse, and other adverse events such as falls or other accidents. In 2016 the US FDA issued a warning against the coincident use of benzodiazepines and opioids. Benzodiazepines are contributors to the current "Opioid Crisis" that claimed the lives of ca. 72,000 persons in the USA in 2017. With the exception of benzodiazepines there are few other options available for the "as needed" *pro re nata* (prn) treatment of anxiety, except for Hydroxyzine and off-label beta blockers that are often prescribed for performance anxiety.

The autonomic nervous system responds to external stimuli and affects both neurologic and endocrine factors to produce anxiety-related symptoms. Therefore, the biochemical pathways of the beta-adrenergic (i.e., beta 1) and muscarinic (i.e., M1 and/or M2) receptors are appropriate molecular targets for the pharmacologic regulation of the symptoms of anxiety. The symptoms of acute anxiety include tachycardia, palpitations, hyperventilation, dyspnea, increased blood pressure, anxiousness, nervousness, fear, avoidance, nausea, vomiting,

* Corresponding author.
E-mail addresses: armand323@hotmail.com (A.B. Benjamin), tom@tomdooley.org (T.P. Dooley).

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tremors, ruminating thoughts, and sweating. These symptoms are under the control of both the sympathetic and parasympathetic autonomic nervous system, which are affected by beta blockers and antimuscarinic (motion sickness) agents, respectively.

Compounded PanX® Atenolol 25 mg–Scopolamine HBr 0.2 mg has been shown in recent physician-sponsored case series reports to be beneficial as a prn anxiolytic treatment [2–5]. In addition, another physician-sponsored study has demonstrated effectiveness in situational anxiety in patients undergoing a medical procedure [6]. However, only three of those patients were evaluated and treated by a board certified psychiatrist; the remainder were evaluated and treated in a pain management setting. Therefore, the present physician-sponsored study sought to better understand the effects of this compounded medication in a larger sample of patients evaluated and treated in a residential rehabilitation and psychiatric setting. These patients have complex psychiatric conditions and medical histories. Some have been on multiple psychiatric medication regimens and/or have had experiences with substance abuse. Thus, they are to be considered as "difficult-to-treat" psychiatric patients.

2. Methods

Eight adult patients (male and female) were evaluated and treated by a psychiatrist in a residential treatment center, Seasons Malibu in California. All patients provided written informed consent to participate in a physician-sponsored study of compounded Atenolol–Scopolamine for the prn treatment of their anxiety symptoms.

Compounded therapies, including drug combinations, can be legally dispensed to patients in need of a treatment, albeit subject to regulatory oversight by State Boards of Pharmacy and the US FDA. Compounded medications are not FDA-approved products. The Atenolol 25 mg–Scopolamine HBr 0.2 mg tablets were prepared in a compounding pharmacy under 503A regulations (Pine Pharmacy, Buffalo, NY). They were produced in troche tablet molds, intended as orally disintegrating tablets (ODTs). The excipients included PCCA Polyglycol Troche mix (sweetened), Steviol glycosides, mannitol, and silica gel. However, the patients administered the tablets by oral ingestion in this study.

The primary anxiolytic endpoint is a numerical self-assessment of the level of anxiety symptoms using the Beck Anxiety Instrument (BAI) [7]. This assessment instrument was chosen in view of its emphasis on somatic symptoms of anxiety. The paper-based questionnaire has 21 items each scored from 0 points (not at all) to 3 (severe), and the aggregate scores range from 0 to 63 points. Therein, 0–9 is considered normal; 10–18 is mild-to-moderate anxiety; 19–29 is moderate-to-severe anxiety; and 30–63 is severe anxiety. However, in this physician-sponsored study the "State" anxiety was obtained at the time of assessment, rather than the "Trait" anxiety for the cumulative week prior to assessment. This minor modification of the BAI instrument regarding timing (hereby termed as "BAI-S") was used in assessments prior to (pre) and one hour (1 h post) and approximately 4 h (~4 h post) following oral drug administration.

The cardiovascular endpoints included blood pressure (systolic and diastolic) and heart rate obtained during a subset of the treatment sessions (pre, 1 h post, and 4–5 h post). Also a custom questionnaire was used to assess patient symptoms (e.g., calming effect, onset, duration, subjective anxiety level on a 0–10 point scale) and side effects (e.g., dry mouth, sleepiness). The psychiatrist also reviewed the data with each patient to clarify efficacy and tolerability.

3. Results – patient summaries

The diagnosis, evaluation, and history for each of the eight adult patients is summarized:

Patient # 04 – A 23 year old Caucasian male with a long chronic history of PTSD, Major Depression, and Generalized Anxiety. This patient reported being on *"everything in the books and nothing works"*. As mood instability was his most prominent symptom, he was started on Lurasidone and Gabapentin, but felt neither were effective. Multimodal therapies allowed for improvement overall, but he felt his anxiety was most problematic. A trial of PanX® Atenolol–Scopolamine was initiated and he felt *"this medication has been the only medication that I have noticed a real difference"*. His BAI-S dropped from 29 to 10 at one hour. He experienced a calming effect within 20 min without side effects with the duration of effect in the 6–8 h range. Subjectively, he felt his subjective anxiety drop from an 8–9/10 to a 2/10.

Patient # 05 – A 23 year old Caucasian male with prominent Social Anxiety, who would use opiates to self-medicate. He was stabilized on Gabapentin for Social Anxiety and Generalized Anxiety Disorder, and Trazodone for sleep, but requested a trial of PanX® Atenolol–Scopolamine for breakthrough anxiety. His BAI-S dropped from 24 to 5 at one hour with the perception of anti-anxiety effect taking 45 min and drops of anxiety from the 7/10 to 3/10 range and lasting four hours. He did express some fatigue after taking the medicine, but denied having negative functional effects.

Patient # 06 – A 36 year old Caucasian male with diagnoses of Opioid Use Disorder, Benzodiazepine Use Disorder, and Generalized Anxiety Disorder was initially detoxed successfully and stabilized with Fluoxetine 20 mg once daily, Mirtazapine 30 mg at night, and Trazodone 300 mg at night. He had a previous trial of Gabapentin, which did not help his acute anxiety, and was tried on Hydroxyzine 50 mg as needed for anxiety, which did not work. PanX® Atenolol–Scopolamine was initiated and his BAI-S score dropped from 13 to 0 at ~4 h. He described the medication as working *"as well as any benzo"*. He described onset within 50 min, duration of effect in the 6–8 h range, and on average, subjective anxiety drops from a 5/10 to a 0/10. He did experience some dry mouth and mild sedation, which did not limit functioning.

Patient # 07 – A 24 year old Caucasian female with a long history of chronic PTSD, Major Depression, Generalized Anxiety, and Social Anxiety, who would use alcohol as a coping strategy. She was stabilized on Levomilnacipran 40 mg daily, Gabapentin 900 mg thrice daily for anxiety prevention, and Doxepin 20 mg at night for sleep. As she felt the Gabapentin did not help her breakthrough panic attacks, PanX® Atenolol–Scopolamine was initiated. She noted a benefit within 20–30 min, and a drop in subjective anxiety score from 8–9/10 to 4–5/10. She compared it to Alprazolam (a benzodiazepine) as having a calming effect without a "high feeling". She endorsed some mild sedation. Her BAI-S dropped from a 20 to 2 at approximately 4 h, and duration of effect was in the 6–8 h range.

Patient # 08 – A 46 year old Caucasian male with diagnoses of Major Depression, Generalized Anxiety, and Social Anxiety was stabilized on Bupropion XL 150 mg once daily, Gabapentin 600 mg three times a day, and Olanzapine 5 mg at night. Although he felt much improved, he felt cannabis was the only thing that decreased his anxiety, and as he chose to be cannabis-free, a trial of PanX® Atenolol–Scopolamine was started. His BAI-S dropped from 13 to 2 at approximately four hours, his perceived subjective anxiety from a 5/10 to 3/10, with calming onset within 45 min and felt like it lasted about 2 h. His side effects included dry mouth and some mild sedation, but denied any functional impairment.

Patient # 09 – A 44 year old Caucasian female with Major Depression, Generalized Anxiety, and Social Anxiety, was stabilized on Fluoxetine 40 mg daily and Mirtazapine 7.5 mg once at night. Overall, Pregabalin 75 mg twice a day would reduce her baseline anxiety. However, her anxiety would spike when dealing with relationship stressors. PanX® Atenolol–Scopolamine was initiated and she noted her anxiety levels dropped subjectively from an 8–9/10 to 2/10, with a calming effect within 20 min. She felt the positive response was similar to prior use of Lorazepam (a benzodiazepine). She denied any dry mouth or impaired vision. She did note some mild sleepiness and a headache, but these were well tolerated as she desired to continue on

the medication on an as needed basis. Her BAI-S dropped from 17 to 6 at one hour with an anxiolytic effect lasting 4–6 h.

Patient # 10 – A 53 year old Caucasian female with a diagnosis of Major Depression with late onset with post-menopausal linkage, and Generalized Anxiety, was stabilized on Sertraline 200 mg per day, tapering off Venlafaxine XR 37.5 mg qam, Lurasidone 40 mg at night, and l-Methylfolate 7.5 mg daily. She did have some breakthrough anxiety and did not feel PanX® Atenolol–Scopolamine was effective, but her scores reflect inconsistent mixed results. She also noted her anxiety initially improved on PanX®, and then got worse during a facial (beauty treatment). She denied any side effects. Her BAI-S dropped from 12 to 5 at one hour, but she did not feel it helped, she declined to continue it upon discharge. She was deemed a non-responder to the medication.

Patient # 11 – A 24 year old Caucasian female with a diagnosis of Bipolar II was discharged on a complex medication regimen, including Quetiapine 50 mg at night, Lamotrigine 200 mg daily, Duloxetine 60 mg daily, Methylphenidate ER 36 mg daily, and Clonazepam 1 mg (a benzodiazepine) three times a day. She acknowledged abusing Clonazepam in the past and was willing to give PanX® Atenolol–Scopolamine a trial. She disliked that it dissolved in the oral cavity and/or was chewable; it was designed as an orally-disintegrating tablet. She felt it did not lessen her anxiety, and increased her fatigue. Her BAI-S score dropped from 8 to 7 at approximately 4 h, but her questionnaire reflected a subjective 4 point drop on a 10 point scale (6–2) in anxiety after 1 h. Her questionnaire denied any side effects. When asked to clarify, she felt in conclusion it did not help and declined it on discharge. She was deemed a non-responder to the medication.

3.1. Results – anxiolytic and cardiovascular effects

The results of oral Atenolol–Scopolamine in the eight patients are summarized in Table 1. Six of the eight patients were deemed as responders, defined as those with a self-perceived subjective calming effect and a reduction in their BAI-S scores post-administration at 1 h and/or approximately 4 h. The mean (average) of the BAI-S scores for all eight patients, including two non-responders, were 15.9 (7.7 SD) at baseline pre-treatment, 8.5 (4.3 SD) at 1 h post-treatment, and 4.1 (4.3 SD) at approximately 4 h post-treatment. For the six responders the BAI-S scores were 16.9 (8.2 SD) at baseline, 9.0 (4.4 SD) at 1 h post-treatment, and 2.6 (2.9 SD) at approximately 4 h post-treatment. The mean BAI-S assessment times of the "1 h" period was 64.4 min (9.6 min SD) and the "approximately 4 h" period was 233 min (48.5 min SD).

The self-perceived calming effect was noted in the six responders (and inconsistently in another patient, # 10, deemed as a non-responder). The mean of the subjective anxiety level in the six responders was 7.1 points (1.7 SD) prior to oral dosing versus 2.4 points (1.5 SD) post-treatment, on a 0–10 scale. The onset of the calming effect from an oral dose was first perceived within 15–60 min in seven patients, with a duration of 2–8 h in the six responders. The side effect of mild sleepiness (mild sedation) was noted in six patients, all of whom were coincidentally also taking other anxiolytic prescription medications.

Table 2
Anxiolytic and Cardiovascular Effects of Atenolol–Scopolamine (Means).

Assessment/Time	Pre	Post 1 h	Post ~4 h	Post 4–5 h
BAI-S State Anxiety	15.9	8.5	4.1	–
Heart Rate (bpm)	93.6	77.0	–	79.7
Blood Pressure Systolic (mmHg)	122.9	112.8	–	104.4
Blood Pressure Diastolic (mmHg)	77.7	72.4	–	71.7

Heart rates and blood pressures (BP) were determined at the time of drug administration (pre-treatment) and following administration (post-treatment) at 1 h in 12 separate treatment episodes within six patients, including one treatment episode of a non-responder. The results are summarized in Table 2. Heart rates and BPs were also determined for a subset of these treatment episodes (n 9) at 4–5 h post-treatment. The mean (average) heart rates were 93.6 bpm (12.8 SD, n 12) pre-treatment, 77.0 bpm (14.6 SD, n 12) at 1 h post-treatment, and 79.7 bpm (14.0 SD, n 9) at 4–5 h post-treatment. Thus, there was a reduction in mean heart rate of 16.6 bpm at 1 h and 13.9 bpm at 4–5 h following drug administration. The reduction in heart rate at 1 h and 4–5 h positively correlates with a reduction in State anxiety (BAI-S and calming effect) at 1 h and ~4 h.

The mean systolic BPs were 122.9 mmHg (10.0 SD, n 12) pre-treatment, 112.8 mmHg (15.5 SD, n 12) at 1 h post-treatment, and 104.4 mmHg (8.9 SD, n 9) at 4–5 h post-treatment. The mean diastolic BPs were 77.7 mmHg (8.0 SD, n 12) pre-treatment, 72.4 mmHg (12.2 SD, n 12) at 1 h post-treatment, and 71.7 mmHg (9.5 SD, n 9) at 4–5 h post-treatment. Thus, the mean blood pressures dropped from 122.9/77.7 mmHg to 112.8/72.4 mmHg at 1 h post-treatment and further to 104.4/71.7 mmHg at 4–5 h post-treatment by Atenolol–Scopolamine HBr. In other words, there were reductions of 10.1 mmHg systolic and 5.3 mmHg diastolic at the one hour time point, and even greater reductions at the later time point. Thus, reductions in both systolic and diastolic BP at 1 h and 4–5 h positively correlate with reductions in State anxiety (BAI-S and calming effect) at 1 h and ~4 h.

4. Conclusions & discussion

Prior to this physician-sponsored study other clinical reports on

Table 1
Summary of Anxiolytic Effects of Atenolol–Scopolamine in 8 Psychiatric Patients.

Patient	BAI-S Pre	BAI-S 1 h	BAI-S ~4 h	Calming Effect	Calming Onset	Calming Duration	Side Effects	Other Anxiolytic
04	29	10	9	yes	20 min	6–8 h	no	no
	8	6	2					
	11	6	2					
05	24	5		yes	45–60 min	4 h	sleepiness	gabapentin
	31	14						
	21	16						
06	13		0	yes	50 min	6–8 h	dry mouth, sleepiness	fluoxetine
	10		0					
	6		4					
07	20		2	yes	20–30 min	6–8 h	sleepiness	levomilnacipran, gabapentin
08	13		2	yes	45 min	2 h	dry mouth, sleepiness	gabapentin
09	17	6		yes	20 min	4–6 h	dry mouth, sleepiness	fluoxetine, pregabalin
10	15		13	uncertain	15–60 min		no	sertraline, venlafaxine
	12	5						
11	8		7	no			sleepiness	duloxetine, clonazepam
Mean	**15.9**	**8.5**	**4.1**					
SD	7.7	4.3	4.3					

compounded PanX® Atenolol 25 mg–Scopolamine HBr 0.2 mg were published. Three patients diagnosed by a psychiatrist (Ashley Benjamin) with post-traumatic stress disorder (PTSD) and experiencing acute anxiety episodes were treated with Atenolol–Scopolamine HBr [2,3,5]. All three patients reported a calming effect, with some minor side effects. The calming effect was first experienced within about 20–30 min (one patient tried it sublingually which resulted in beneficial effect within 15 min) with the perceived calming effects lasting in the 4–6 h range.

Another case series included three patients receiving care in a pain management clinic and manifesting with episodes of acute anxiety symptoms, who were treated prn with compounded Atenolol–Scopolamine HBr [4]. All three patients reported a calming effect, with some possible minor side effects. Two of the patients noted rapid symptom resolution within 10–15 min with perceived calming benefits in the 2–6 h range.

Another physician-sponsored study was conducted in a pain management clinic of eight patients experiencing situational anxiety in anticipation of a medical procedure [6]. Within 10–20 min of drug administration of compounded Atenolol–Scopolamine HBr, the patients commenced an electromyography (EMG) procedure. The patients were assessed prior to and during the procedure. Seven of the eight patients reported a perception of a calming effect. Six of the eight patients were deemed as responders to the drug treatment, with an overall subjective anxiety score (10-point scale) from an average of 6.3 points prior down to an average of 2.7 points during the procedure. The six responders also reported quantitative reductions in the number and/or severity of individual anxiety symptoms. None of the eight patients reported experiencing any side effects. All reported being clear minded; none were aware of any impairment of cognition.

In aggregate the prior published physician-sponsored studies (n = 14) plus the present investigation (n = 8) have evaluated and treated 22 patients experiencing anxiety symptoms. Atenolol 25 mg–Scopolamine HBr 0.2 mg has demonstrated a fast-acting and self-perceived calming effect orally within < 60 min or mucosally (orally-disintegrating) within < 30 min. The self-perceived anxiolytic effect was reported by 19 of 22 patients, and 18 (i.e., 82 percent) of whom were deemed as responders. The calming effect persisted for multiple hours, with some patients noting that the self-awareness of the calming effect lasted up to 8 h. It is possible that some anxiolytic benefit endures even longer than the patient's self-awareness of the calming effect.

In this study, the reductions in the Beck Anxiety Instrument – State (BAI-S) scores at one and ~4 h post-treatment provide strong evidence of anxiolytic benefit in difficult-to-treat anxious patients. Furthermore, tachycardia is a common symptom in acute anxiety episodes, and the reductions in heart rate at 1 h post-treatment (16.6 bpm) and 4–5 h post-treatment (13.9 bpm) are positively correlated with the improvement in State anxiety symptoms at 1 h and ~4 h. Similarly BP declined by 10.1 mmHg systolic and 5.3 mmHg diastolic at 1 h, and even more at 4–5 h. The reductions in heart rate and blood pressure at 1 h and 4–5 h are consistent with the anticipated pharmacologic action of the beta blocker Atenolol on the sympathetic autonomic nervous system. A reduction in heart rate was also noted in another psychiatric patient in a prior published case report of this medication [2].

These effects of the combination drug on heart rate and blood pressure can be compared directly to a published controlled clinical study of Atenolol 50 mg and/or Scopolamine HBr 0.3 mg in 12 healthy "normal" subjects, including during exposure to high heat in a sauna [8]. Therein, Atenolol 50 mg (oral) alone at two hours reduced the mean baseline heart rate from 72 bpm to 59 bpm (i.e., 13 bpm reduction). In contrast, Scopolamine HBr 0.3 mg (oral) had little to no effect (i.e., only 2 bpm reduction and within the SD of baseline HR). Furthermore, the heart rate upon co-administration of both oral drugs (57 bpm) mirrored the results of Atenolol alone (59 bpm and within the SD of the co-administration of both drugs). Scopolamine at 0.3 mg oral had little or no effect at two hours and beyond, and thus did not counteract or abrogate the cardiovascular effects of Atenolol on heart rate [8]. This was true while under normal resting conditions or under heat-induced stress. The effects of Scopolamine were negligible, if any, when administered either alone or co-administered with Atenolol. Note the doses in the cardiovascular trial were higher (50 mg and 0.3 mg) than those used in the present physician-sponsored study in psychiatry (25 mg and 0.2 mg).

In the present study of compounded Atenolol 25 mg–Scopolamine HBr 0.2 mg, tachycardic heart rate reduced by 17.7 percent at 1 h, which is a similar level of reduction (i.e., 18.1 percent) of Atenolol 50 mg alone in healthy patients at 2 h in the cardiovascular study [8]. Furthermore, in the cardiovascular study Atenolol 50 mg alone reduced systolic BP at two hours by 10 mmHg [8], which is essentially the same level achieved by the compounded Atenolol 25 mg–Scopolamine 0.2 mg at one hour (10.1 mmHg) in the psychiatric patients affected by anxiety symptoms. These comparisons of BP and HR between the published cardiovascular study and this work with anxious patients in psychiatry provide evidence of a beneficial cardiovascular effect of Atenolol coincident with a reduction in State anxiety in the present study.

The mean of the subjective anxiety level (0–10 point scale) in the six responders in this study was 7.1 points (pre-treatment) to 2.4 points (post-treatment). This is similar or greater than the reduction in subjective anxiety level in the six responders in the medical procedure study from a mean of 6.3 points (pre-treatment) to 2.7 points (post-treatment) [6].

In the current study reductions of this magnitude in both subjective endpoints (e.g., BAI-S and/or subjective anxiety score) and especially objective endpoints (e.g., heart rate, systolic blood pressure, and diastolic blood pressure) are highly unlikely to be due to a placebo effect. It should be emphasized that these patients were familiar with concurrent or prior anxiolytic medicines and/or other abused substances (e.g., alcohol, opioids, or benzodiazepines). In other words, these psychiatric patients already "know" what works for them in view of familiarity with other anxiolytics, including benzodiazepines. An inactive medication is likely to be easily dismissed by this population. In addition, the 82 percent response rate to date (18/22 patients) underscores that this drug combo is effective as an anti-anxiety treatment, albeit prior to evaluation in a placebo-controlled trial.

Three of the patients (#06, 07, 09) commented that PanX® Atenolol–Scopolamine produced a perceived anxiolytic benefit mirroring that of benzodiazepines. This comparison to benzodiazepines has also been made by three other psychiatric patients in the prior published case series [2,3,5]. To yield a benzodiazepine-like perceived benefit, without using a US Drug Enforcement Agency Controlled Substance known to have the potential for dependence and/or addiction, is a desirable attribute of this new medication. There is no history of dependence and/or addiction for either Atenolol or Scopolamine in over five decades of prescription and/or OTC use.

Based upon a review of the clinical literature on beta blockers and antimuscarinic agents, the authors anticipated that this new approach would be beneficial in the treatment of anxiety symptoms related to substance abuse, such as drug or alcohol abuse, withdrawal, and/or addiction. Three of the patients in this study were being treated in the residential setting for substance abuse – patient #07 for alcohol and patients #05 and #06 for opioids. Also individuals who have abused benzodiazepines are in an at-risk population. In 2016 the FDA issued a warning against the coincident use of benzodiazepines and opioids. PanX® medications are promising fast-acting alternatives to benzodiazepines, not only for the treatment of anxiety disorders, but also for anxiety associated with substance abuse and addiction.

The combo drug was expected to be well tolerated and with possible side effects including dryness of the mouth, mild sleepiness (mild sedation), dizziness, bradycardia (< 60 bpm), hypotension (< 90/60 mm Hg), and although unlikely perhaps visual distortion (pupil dilation). Impairment of cognition was not anticipated based upon the historic

literature or published results with Atenolol–Scopolamine. Minor and well tolerated side effects were note in a subset of the patients, such as dry mouth and mild sleepiness (mild sedation). The mild sleepiness occurred in patients who were also taking other anxiolytics. Whether the mild sleepiness is due to the PanX® Atenolol–Scopolamine medicine alone or in combination with other concomitant anxiolytics is not clear. Dryness of the mouth was noted in three patients. Whether dry mouth was due to the medication (especially Scopolamine) or in combination with other concomitant anxiolytics is not clear. Note that dry mouth is a common manifestation of acute anxiety episodes (e.g., panic attack), so that it might not reflect a drug-related side effect in some patients. Regardless, all of the side effects were well tolerated. None of the side effects were unanticipated with regard to the historic side effect profiles for either Scopolamine or Atenolol as monotherapies.

Several limitations to this study may be noted. First, physician-sponsored studies typically do not include a placebo control, whereas a placebo is usually included in FDA registration trials. The study was limited to eight Caucasian male and female adults treated in a single facility on the West Coast of the USA. Future research could allow for other racial, ethnic, cultural, regional, socioeconomic, and age backgrounds, although there is no reason to believe that Atenolol–Scopolamine HBr would not be equally effective in the broader context.

It should be noted that the selected doses for both active ingredients are “low” in this compounded drug combination of Atenolol 25 mg–Scopolamine HBr 0.2 mg. Atenolol is routinely prescribed for hypertension or other cardiovascular conditions at oral doses of 25–100 mg [9]. The recommended starting dose for hypertension is typically 25 mg. Scopolamine is approved over-the-counter (OTC) for motion sickness in many countries outside of the USA (e.g., Australia, Europe, UK, and Canada) at 0.3 mg [10]. The foreign OTC is available for use in children at half of this dose (0.15 mg). For any drug to receive an OTC registration, it must be considered to be very safe by the regulatory agency, albeit subject to the dosage, route of administration, and frequency of administration. The selected “low” doses for this particular PanX® drug combination have been historically safe for each agent as oral monotherapies.

A lack of anxiolytic response in ca. 18% of the 22 treated anxious patients (published and this work) might be due to differences in pharmacokinetics (ADME), pharmacologic receptor sensitivity, and/or the “low” doses used in this fixed-dose combination. It is possible that the two patients deemed to be non-responders (#10 and #11) in this study might respond via mucosal delivery (oral mucosa of orally disintegrating tablets) and/or to higher doses of this oral medication.

Human clinical studies have provided evidence that Atenolol can produce some benefit with regard to the symptoms of acute anxiety. For instance, Atenolol that has been used to suppress performance anxiety when administered orally in advance [11]. It has also been shown to be beneficial in alcohol withdrawal and flight phobia [12–15]. In a placebo-controlled trial Atenolol was found to be moderately effective against Social Anxiety Disorder [16]. In another placebo-controlled trial the pre-treatment of patients with Atenolol two hours prior to a medical procedure (nasal speculum insertion) reduced the procedure-related increase in tachycardia and mean arterial pressure [17]. Atenolol is a preferred beta blocker, as it is a beta-1 selective peripheral-acting agent, which should reduce the risk for asthmatic and COPD subjects relative to the non-selective beta blockers (e.g., propranolol) [18,19].

In view of these clinical reports, off-label Atenolol alone can provide some symptomatic relief with regard to performance anxiety. However, beta blockers alone do not sufficiently address the aggregate symptoms of acute anxiety, and especially the Central Nervous System (CNS)/psychic symptoms thereof. Thus, there is a need to couple a beta-blocker with another type of active ingredient to affect the CNS and other symptoms.

Scopolamine (also known as Hyoscine) is commonly used for the treatment of motion sickness, nausea, and vomiting. The mechanism of action of this antiemetic drug is as an antagonist of muscarinic acetylcholine receptors. Scopolamine HBr has been delivered to adults sublingually (mucosally) at 0.15 mg/dose [20], orally at 0.3–1.0 mg/dose [10,21,22], and transdermally at 0.5 mg/day for 3 days for motion sickness. Scopolamine was known over a century ago to produce a calming effect in psychiatric patients [23], although this pharmacologic property is not well known today among medical providers. There is also evidence that Scopolamine can exhibit an antidepressant property after multiple days in Major Depressive Disorder [21,24–26]. Furthermore, a human genetic study of the muscarinic acetylcholine receptor M2 (*CHRM2)* gene have revealed an association between specific genetic polymorphisms and the risk of depression in major depressive syndrome [27]. Scopolamine is a high potency muscarinic receptor antagonist that likely affects anxiety and/or mood via the M2 and/or M1 receptors of the CNS [28].

In view of this information, inclusion of an antagonist of the muscarinic receptor(s) along with a beta blocker in the combination therapy for anxiety disorders is expected to provide safety advantages relative to benzodiazepines. The symptoms of the autonomic nervous system (sympathetic and parasympathetic) that are likely to be alleviated by the PanX® combo include tachycardia, palpitations, increased blood pressure, nausea, vomiting, anxiousness, fear (phobias), avoidance, ruminating thoughts, aberrant breathing, sweating, tremors, and one might speculate possibly migraine and headache.

Based upon the prior case series reports (n = 14 patients) and this study (n = 8 patients) conducted in a residential psychiatry setting, one may reasonably conclude that possible Indications for the Atenolol–Scopolamine drug combination include Social Anxiety Disorder (social phobia), anxiety associated with PTSD, medical and/or dental procedures, Panic Disorder +/− Agoraphobia, Generalized Anxiety Disorder, Specific Phobias (e.g., travel phobia), and anxiety associated with Substance Abuse (e.g., drug or alcohol addiction and/or withdrawal). A fast-acting non-benzodiazepine alternative would be welcome in psychiatry, pain management, medical/dental procedures, and other medical disciplines.

Conflict of interest

Dr. Benjamin reports other from TPD LLC (i.e., consultant and shareholder), during the conduct of the study. Dr. Dooley reports other from TPD LLC (i.e., employee and shareholder), during the conduct of the study; In addition, Dr. Dooley is the inventor of patents US 9,446,030, US 9, 517,231, and US 9, 616,052, an International PCT application, and Canada patent 2,955,575, all with royalties paid to TPD LLC.

Acknowledgement and disclaimers

Dr. Benjamin is a practicing psychiatrist in Ventura County, California. He is also a consultant to Trends in Pharma Development LLC (Birmingham, AL). Dr. Dooley of Trends in Pharma Development LLC is the inventor of PanX®. For PDF files of prior publications on PanX® Atenolol–Scopolamine see: www.TomDooley.org/scientific-publications.html. The authors thank Dr. Sheila Shilati and the staff of Seasons Malibu (Malibu, CA) for their assistance in facilitating this physician-sponsored study. The authors are also grateful to Pine Pharmacy (Buffalo, NY) for filling the prescriptions for compounded Atenolol–Scopolamine HBr. The physician-sponsored study was not supported by any grants or contracts.

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