

CONSUMER'S KNOWLEDGE OF ENERGY DRINK INGREDIENT  
INTERACTION WITH THEIR PRESCRIBED  
PSYCHOTROPIC MEDICATIONS

by

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DEDICATION

For Andy, who has navigated with me the many life events that have occurred in our family over the course of my studies, plus has had to live in the shadow of “the thesis”, I love you more than you’ll ever know. May you always be a life-long learner, just like grandma and grandpa, and me.

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## ABSTRACT

Each of the 300+ energy drinks currently on the market has a unique mixture of ingredients. Little is known whether consumers know what ingredients are in their drinks, especially those consumers who also take medications. Particularly consumers who take psychiatric medication can be at risk for adverse events due to potential drug/ingredient interactions. The purpose of this study was to examine energy drink consumer's knowledge of potential ingredient interactions with their mental health medications. In this study, 67% of respondents ( $n=6$ ) stated they were not aware of any interactions between their psychiatric medications and the ingredients of their energy drinks. An unexpected finding emerged when all respondents made unsolicited comments about their energy drinks being "bad", although this did not deter them from consumption. If these results are replicated in further studies with larger and more diverse samples, a targeted education initiative for consumer safety could be developed.

## INTRODUCTION

Energy drink consumption has burgeoned exponentially with global sales worth USD \$39.8 billion in 2013 and expected sales reaching USD \$61.7 billion by 2021 (Research and Markets, 2015). While the advertising for energy drinks emphasizes such things as increased energy, alertness, and enhanced physical and mental performance, little is known about consumer's knowledge of the ingredients present in the drinks. A lack of ingredient knowledge is particularly concerning for those consumers who ingest energy drinks as well as take prescribed psychotropic medications. If consumers are not aware of the possible interactions, they may inadvertently place themselves in harm's way through possible potentiation or inhibition of those medications. A review of the literature was done to gain further insight into consumer's knowledge of these potential risks. To gain a better understanding of psychiatric patient's knowledge of potential interactions between their medications and the ingredients of their energy drinks, semi-structured interviews were conducted.

### Background

Energy drinks are “flavored beverages containing high amounts of caffeine and typically other additives, such as vitamins, taurine, herbal supplements, creatine, sugars, and guarana...” (Substance Abuse and Mental Health Services [SAMSHA], 2013). Other common ingredients include four caffeine containing compounds: guarana, yerba mate, yohimbine, and kola nut; as well as B vitamins, ma huang, ginseng, *L*-carnitine, ginkgo biloba, inositol, glucuronolactone, and creatine. (McLellan & Lieberman, 2012; Smoyak,

2015; Smoyak, Nowik, & Lee, 2015; Ishak, Ugochukwu, Bagot, Khalili, & Zaky, 2012; Heneman & Zidenberg-Cherr, 2007.)

Reasons for using energy drinks include: compensating for insufficient sleep, promoting wakefulness, desire to increase energy, to boost performance during exercise, for taste, to mix with alcohol, and for concentration enhancement (Attila & Çakir, 2011; Aslam et al., 2013; Babwah, Maharaj, & Nunes, 2014; Malinauskas, Aeby, Overton, Carpenter-Aeby, & Barber-Heidal, 2007; Kim, Y. J., Jeon, Shim, & Seo, 2015; Ali, Rehman, Babayan, Stapelton, & Joshi, 2015).

There are more than 300 varieties of energy drinks and shots available in the United States (Heckman, Sherry, & DeMejia, 2010) with the market share in 2015 comprised of Red Bull®, Monster®, Rockstar®, Amp®, and NOS® (Caffeine Informer, n.d.) The caffeine content in energy drinks ranges from 80 milligrams (mg) to more than 500 mg per container. This is in comparison with a 5-ounce (oz) cup of brewed coffee which contains about 100 mg, a 12-oz can of soda up to 90 mg, and a 20-oz bottle of soda which ranges upwards to 121 mg (Caffeine Informer, n.d.). Some energy shots, (defined as beverages concentrated into 3 oz or less), contain caffeine in excess of 100 mg per fluid ounce (Reissig, Strain, & Griffiths, 2009). 5 Hour Energy® was the top seller in the energy shot market in the United States (US) in 2015 and contains 200 mg per 1.93 fluid ounce (Caffeine Informer, n.d.). Both energy drinks and shots are readily accessible for purchase and have no age restriction for purchase.

Energy drinks entered the United States market in 1997, with the introduction of the Austrian-import Red Bull® (Dolan, 2005). Through the use of directed product placements, youth-oriented social media, celebrities, and sponsored events, marketing is

heavily directed towards youth and young adults. Although reduced from previous years, \$175 million was spent in 2013 advertising energy drinks with exposure to those advertisements beginning as early as preschool (Yale Rudd Center, 2011). Market surveys from Mintel International Group Ltd. reveal that 31% of 12 to 17, 34% of 18 to 24, and 22% of 25 to 34-year-olds report regular consumption of energy drinks (March, 2007). In a 2013 study by Cotter et al., 58% of young adults admitted to drinking an average of 2.6 energy drinks per day over the last 30 days. Gender also plays a role in consumption with boys and men consuming more than girls and women (Ogden, Kit, Carroll, & Park, 2011).

Contrary to the current marketing strategies, data from a more recent Mintel survey shows a significant trend change in consumer age. Older Millennials (those born between the early 1980's to early 1990's) are now "the core consumers of the US energy drink/shots market, with 64% consuming energy drinks." Parenthood is having an effect on energy drink consumption. Households with children were significantly more likely to consume energy drinks, compared to those without, attributing this change to "lifestyle shift(s)..., as a result, their interests and priorities are shifting and individuals that require more energy are turning to energy drinks and shots..." as options alongside other caffeine beverages such as coffee and carbonated soft drinks. (Mintel International Group, Ltd., 2015).

Responses to a 2015 Harris Poll revealed two-thirds of US adults believe alternative treatments (i.e., chiropractic care, massage therapy, and herbal remedies) are safe and effective. 50% said they would be likely to use an alternative treatment in addition to, or instead of, conventional western treatment to treat or manage a mental health condition, with responses increased to 75% when depression was specified as the mental health

condition (Harris Poll, 2015). While interest in natural offerings may stem from perceptions that natural/organic products are healthier, concerns about safety do not seem to have a significant impact on usage. The aforementioned 2015 Mintel survey found “a growing popularity of natural claims in the category with 30% of users consuming natural energy drinks/shots.” However, “Consumers are not leaving regular energy drinks/shots for natural but are drinking both... The development of products that promote themselves as healthy/better-for-you will influence the expansion of the energy drink market.” (May 2015).

Despite consumer's anticipation of beneficial effects, there are risks involved with energy drink consumption that consumers have been slow to learn. Major adverse effects including destabilization of mood, exacerbation of manic phases, restlessness, tremors, anxiety, agitation, seizures, blood pressure and electrocardiogram changes, and sleep disruption (Ali et al., 2015; Clausen, Shields, McQueen, & Persad, 2008; Babu, Church, & Lewander, 2008; Chelben et al., 2007; Iyaduria & Chung, 2007; Fletcher, Lacey, & Shah, 2014; Wesensten, 2014). Consumption has also led to increased utilization of health care services, increased cost of care, decreased quality of life, and has been linked to a number of deaths (SAMSHA, 2014; Ali et al., 2015; Ishak et al., 2012; Reissig et al., 2009; Bramstedt, 2007; Center for Food Safety and Applied Nutrition [CFSAN], 2012). No safe levels of consumption have been established for children, adolescents, or young adults (Seifert, Schaechter, Hershorin, & Lipshultz, 2011).

Along with adverse physical effects, a number of risk-taking behaviors have been associated with frequency of energy drink consumption. These include participating in extreme sports, taking risks on a dare, sexual risk-taking (e.g., unprotected intercourse,

having intercourse under the influence of alcohol or drugs), failure to wear seatbelts (Miller, 2008), drunk driving, and riding in a car with an inebriated driver (Spierer, Banding, & Santella, 2014). An association with nonmedical use of prescription stimulants has also been found (Arria et al., 2010; Woolsey et al., 2014; Miller, 2008; Miller & Quigley, 2011), as well as use of ecstasy, marijuana, and increased tobacco use (Trapp et al., 2014; Arria et al., 2010). The interested reader can also read Arria, Bugbee, Caldeira, and Vincent's (2014) summary of studies related to risk-taking behaviors.

A further risk of note is related to the mixing of energy drinks with alcohol. "Wide-awake drunkenness" is described as the stimulating effects of the energy drink masking the intoxicating effects of the alcohol. The resulting inability to accurately assess one's true level of impairment can lead to poor decision making and engaging in risky behaviors (Arria & O'Brien, 2011; Peacock et al., 2015).

Prior to 2010, caffeinated alcoholic beverages could be found in retail stores. The only restriction was being of legal age for purchasing alcohol. Safety concerns involving the combination of energy drinks with alcohol prompted Arria and O'Brien (2009) to request the U.S. Food and Drug Administration (FDA) remove caffeine's GRAS status when used as an additive to alcoholic products. This resulted in an effective ban on retail sales and marketing of any alcoholic products that had caffeine directly added as a singular ingredient (U.S. Food and Drug Administration [FDA], 2010; Arria & O'Brien, 2011).

Although pre-mixed drinks are no longer sold in stores, energy drink/alcohol combinations continue to be quite popular. One such combination sold at local bars is the mixture of vodka with Red Bull®. Other combinations are mainstream enough to have names such as "Bull Blaster" (Jaeger®+Red Bull®), "Vegas Bomb" (Crown® peach

schnapps+Malibu®+Red Bull®) and the “Chuck Norris” (cherry McGillicuddy® +Blue®). (E. McRae, personal communication, April 17, 2017).

Because energy drinks are not considered pharmaceutical, they are not under the same FDA safety regulations as medications. Instead, as nutraceuticals, the manufacturers themselves make the choice to label them as either a dietary supplement or a conventional food/ beverage. This important distinction affects the type of required regulation and oversight by the FDA, structure and content of ingredient listing on the product, and clarity of total caffeine content.

If designated a dietary supplement, the drink's regulation falls under the auspices of the Dietary Supplement Health and Education Act (DSHEA) of 1994. Examples of dietary supplements are those products that contain “vitamins, minerals, amino acids, and herbs or botanicals, as well as other substances that can be used to supplement the diet” (FDA, 2015, July 15). The FDA only monitors post-marketing safety and labeling accuracy of the ingredient content, not the quantities or combinations of ingredients used. “A manufacturer does not have to prove the safety and effectiveness of a dietary supplement before it is marketed. A manufacturer is permitted to say that a dietary supplement addresses a nutrient deficiency, supports health, or is linked to a particular body function (e.g., immunity) if there is research to support the claim. Such a claim must be followed by the words "This statement has not been evaluated by the U.S. Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease" (National Center for Complementary and Integrative Health [NCCIH], 2014; FDA, 2016, January 13).

Looking at the label informs the consumer which designation the manufacturer

chose for their product. Products designated as dietary supplements will have a Supplement Facts Panel within its product label. The panel must list all ingredients in descending order by weight. If the ingredient is part of a proprietary blend (as is often the case for energy drinks), its singular weight does not need to be listed. “DSHEA provides that when the dietary ingredients in a supplement are considered to be a proprietary blend, just the total amount of the blend need be stated. In the absence of individual amounts, FDA requires that the dietary ingredients in a proprietary blend are to be listed in order of predominance by weight”. Not disclosing the exact amount preserves the proprietary nature of the blend. If any ingredient originates from a plant, the label must identify the part of the plant used (for example leaf, flower, root). If the caffeine is a natural component of a plant used as part of a proprietary blend, only the part of the plant utilized need be listed, not its exact quantity. Total caffeine content does not have to be fully disclosed (FDA, 1999, January 4).

Conversely, if the manufacturer chooses to categorize the drink as a conventional food/beverage, its safety monitoring falls under the Nutrition Labeling and Education Act (NLEA) of 1990 (FDA, 2014, November 25). Products labeled as a conventional food/beverage will have a Nutrition Facts Panel on its label. All panels must list the five core nutrients (calories, total fat, sodium, total carbohydrates, and protein), as well as calcium, iron, vitamin D, and potassium. If there are added or voluntarily declared nutrients, they must also be included on the panel. Excluding calories, each nutrient must have an exact amount listed as either mg or grams (g), along with the percent Daily Value (%DV) per serving.

Declaration of caffeine as an ingredient occurs when the caffeine is added to the

beverage as a compound no longer in its natural form. It has "Generally Recognized As Safe" (GRAS) status “when used in cola-type beverages up to a level of 0.02% or 200 parts per million” (FDA, 2017, August 8), which equates to about 71 mg/12 oz. Current law does not require the precise amount of caffeine to be listed on the beverage label, just that it is present (Mattia, 2013).

The manufacturer's designation highlights an important distinction between the dietary supplement and the conventional food/beverage classification in regards to safety reporting. For dietary supplements, the DSHEA has only minimal safety controls on the front end of supplement production and sales, but more stringent post-distribution reporting and monitoring requirements. For the conventional food/beverage under NLEA, so long as the ingredients used are already FDA pre-approved as a food additive and/or are on the list of GRAS compounds, there are no reporting requirements for serious adverse events post-distribution. Having these two options, the manufacturers can then decide the type, timing, and amount of regulatory oversight they wish for their product.

Prior to 2014, safety oversight of energy drinks was scattered and disjointed due to the nebulous nature of how they were labeled and which regulations applied. Effective 2014, member companies of the American Beverage Association (ABA), which include the companies that provide about 95% of the energy drinks on the market, agreed to a set of labeling and marketing commitments which include categorizing energy drinks as conventional foods/beverages, not as dietary supplements, and listing the total amount of caffeine (from all sources) on the Nutrition Facts Panel (ABA, 2014). Through the use of pre-approved/GRAS ingredients and the oversight of the FDA through NLEA, this seems like a positive step towards consumer safety. However, it also exempts manufacturers

from having to report any post-distribution safety concerns, leading to less information easily accessible to the general public.

Although individual compounds on the pre-approved and GRAS lists are considered "safe under the intended conditions of use" (FDA, 2009, December), there are no requirements for manufacturers of either dietary supplements or conventional foods/beverages to provide safety data on the mixtures or combinations of the particular ingredients used in their energy drinks. There are also no requirements for disclosure of potential ingredient interactions with medications.

Past research and the study of chemical compounds have established that many herbs and supplements interact with medications (Alissa, 2014; Hermann & von Richter, 2012; Gurley, Fifer, & Gardner, 2012; Chadwick, 2005; National Center for Complementary and Alternative Medicine [NCCAM], 2012). Although generally perceived as safe, many herbs and supplements are not safe. Reports of adverse effects include allergic reactions, liver, kidney, and/or heart toxicity, mutagenic effects, herb-drug interactions and idiosyncratic reactions, some of which can result in death (Tsai, Lin, Pickard, Tsai, & Mahady, 2012; Brown, 2016).

Of specific relevance to this current study, history has shown that mixing psychiatric medications with certain chemical compounds can alter the medication's metabolism so significantly that a variety of adverse effects, including death, may result. Although this paper does not seek to provide a thorough review of all potentially harmful interactions, an overview of three pertinent examples will provide the historical underpinnings for the necessity of this current research. These three examples are monoamine oxidase inhibitors (MAOI's), cigarette smoking, and caffeine consumption.

In the case of MAOI's, specific dietary restrictions were found to be necessary due to certain foods causing inhibition of the enzyme necessary for tyramine metabolism. With the enzyme blocked, the resulting elevated levels of tyramine lead to tachycardia, tremors, seizures, and hyperthermia as well as life-threatening hypertensive crisis (Robakis & Fahn, 2015; Garcia & Miller, 2017).

The combination of cigarette smoking with either clozapine or olanzapine is the second example. Interestingly it is the polycyclic aromatic hydrocarbons, not the nicotine, which is responsible for the problematic interaction by causing induction of the cytochrome P450 1A2 (CYP 1A2) enzyme. Cigarette smokers need increased levels of medication due to faster clearance of their medicine as a result of this induction. If a smoker reduces the amount they smoke or quits smoking altogether, a reduction of medication dose by 30-50% is required. Otherwise, toxicity may result (Lowe & Ackman, 2010).

The third example is that of caffeine. Also metabolized by the CYP 1A2 enzyme, caffeine most strongly interferes with the metabolism of clozapine and olanzapine. Another medication, fluvoxamine, blocks the clearance of caffeine by 80% and increases its half-life by 500% which could lead to caffeine intoxication (Culm-Merdeck, von Moltke, Harmatz, & Greenblatt, 2004; Jeppesen et al., 1996). Due to its diuretic effects, caffeine could also interfere with lithium excretion, thereby potentially causing what would appear to be a failure of the medication (Broderick, Benjamin, & Dennis, 2005; Carillo & Benitez, 2000). Since caffeine is the main ingredient in energy drinks, it will be reviewed more thoroughly in the literature review.

As history has shown, the information learned regarding these three examples of

psychiatric medication/chemical compound interactions subsequently helped provide life-saving data which then led to enhanced clinician and patient education resulting in safer prescribing practices.

### Problem Statement

This research study developed as the result of a personal discussion between the investigator and a group of psychiatric providers who expressed concern with the extent of some of their patient's consumption of energy drinks. These particular patients were frequently presenting for appointments with complaints of disrupted sleep, severe anxiety, agitation, irritability, heart palpitations, and gastrointestinal problems. The patients attributed these problems to their psychotropic medications and requested changes in doses, or different medications altogether. When asked about caffeine intake, including energy drinks, they seemed surprised to consider that the energy drink might somehow be involved with their symptoms. The following question developed as a result of those provider/patient interactions: "Do those consumers of energy drinks, who also take psychotropic medications, know if there are any interactions between the ingredients of their drink with their medications?"

### Purpose/Significance

The purpose of this study was to examine energy drink consumer's knowledge of potential ingredient interactions with their mental health medications. With the current lack of targeted research regarding this topic, it was anticipated that this information would contribute to the existing literature, as well as increase the overall safety of

patients through future development of educational resources.

### Theoretical Framework

The Precaution Adoption Process Model (PAPM) provides a theoretical framework from which to understand why those who are prescribed psychotropic medications might put themselves at risk by also ingesting energy drinks. As a stage theory, PAPM's goal is “to explain how a person comes to the decision to take action, and how he or she translates that decision into action. For this reason, the PAPM focuses on psychological processes within individuals. As a consequence, the stages prior to action are defined in terms of the mental states that appear to be important, rather than in terms of factors external to the person such as current behavior, past behavior, or some combination of these with the person's mental state (Weinstein, Sandman, & Blaylock, 2008).

“The PAPM identifies seven stages along the path from lack of awareness to action (Figure 1). At some initial point in time people are unaware of the health issue (stage 1). When they first learn something about the issue, they are no longer unaware, but they are not necessarily engaged by it either (stage 2). People who reach the decision-making stage (stage 3) have become engaged by the issue and are considering their response. This decision-making process can result in one of two outcomes. If the decision is to take no action, the precaution adoption process ends (stage 4), at least for the time being. If people decide to adopt the precaution (stage 5), the next step is to initiate the behavior (stage 6). A seventh stage, if relevant, indicates that the behavior has been maintained over time (stage 7). “ (Weinstein et al., 2008).

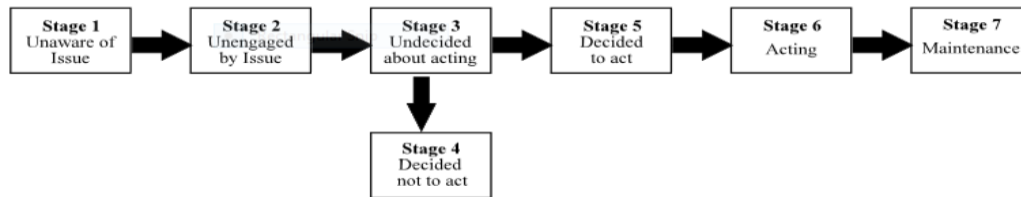


Figure 1. The Precaution Adoption Process Model. Weinstein, N., Sandman, P., & Blaylock, S. (2008). The precaution adoption process model. In K. Glanz, B. Rimer, & K. Viswanath (Eds.), *Health behavior and health education* (pp. 123-147). San Francisco, CA: Jossey-Bass. Retrieved from: <http://www.psandman.com/articles/PAPM.pdf>

The focus of this study is based on PAPM's Stage 1 – “unaware of the issue.” The majority of the energy drink ingredients in question are “natural” and can be individually bought in the health and wellness aisles at any grocery store, pharmacy, or health food store. There exists a perception that by virtue of a product being “natural,” that means it is “safe” (Health Canada, 2011). The cognitive disconnect of not understanding that the ingredients are still pharmacologically active agents places consumers at risk for potential adverse interactions with medications.

## LITERATURE REVIEW

Of the 300+ energy drinks in the US market, each has its own formulation and combination of ingredients. Reviewing every ingredient of every drink is beyond the scope of this research. Attempting to review the vast variety of ingredient combinations is also beyond the scope of this research. According to Sorkin et al.'s (2014) "Executive Summary of NIH Workshop on the Use and Biology of Energy Drinks: Current Knowledge and Critical Gaps," there is only limited peer-reviewed data on the potential for interactions between ingredients in the relatively novel combinations found in caffeine-containing energy drinks. The potential to add to the knowledge base is wide-open for the interested researcher.

This literature review is structured into two sections. Since the top 5 selling drinks in the US market in 2015 were Red Bull®, Monster®, Rockstar®, Amp®, and NOS®, and the top-selling energy shot was 5-Hour Energy® (Caffeine Informer, n.d.), the first section contains a brief overview of each ingredient listed in these six drinks, particularly those listed on the product by each company as their proprietary blend (excluding sweeteners, preservatives, and other flavorings). Concerns regarding potential interactions of each ingredient with psychotropic medications are addressed.

The second section reviews the current information regarding the level of interaction knowledge energy drink consumer's may have. Consideration is given to resulting implications.

### Ingredients

Caffeine. All six of the drinks mentioned above contain caffeine. Caffeine content is also increased in four of the six beverages through the addition of guarana. Three of those four also contains panax ginseng, another additional source of caffeine. The six drinks declare the following total caffeine content:

Table 1 Total Caffeine Content

	mg per serving	serving size – fl oz (ml)	Servings per container	Guarana	Panax ginseng	Total mg per container
Red Bull®	80	8.4 (250)	1			80
Monster®	80	8 (240)	2	✓	✓	160
Rockstar®	80	8 (240)	2	✓	✓	160
Amp®	142	16 (480)	1	✓	✓	142
NOS®	160	16 (480)	1	✓		160
5-Hour Energy®	200	1.93 (58)	1			200

Caffeine is absorbed from the digestive tract and peaks within 45 min – 1 hour with a half-life ranging from 3-6 hours (Wolk, Ganetsky, & Babu, 2012; Broderick & Benjamin, 2004) For healthy adults, the FDA considers up to 400 mg/day “an amount not associated with dangerous, negative effects” (FDA, 2013, May 3). It has GRAS status “when used in cola-type beverages up to a level of 0.02% or 200 parts per million” (FDA, 2017, August 8; FDA, 1978), which equates to about 71 mg/12 oz (FDA Caffeine, 2017). Metabolism of caffeine is extremely variable depending on age, sex, daily exposure to

caffeine, inducers or inhibitors of CYP 1A2, rapidity of consumption, and physical activity (Ali et al., 2015; Higgins, 2010). Doses above 750 mg have been shown to trigger panic attacks in healthy adults (Broderick & Benjamin, 2004). Caffeine is lethal above 10 g (Yew & Byrns, 2017) or amounts above 170 mg/kg (FDA, 1978).

Caffeine exerts its action on the body through four main mechanisms: 1- nonselective antagonism of adenosine receptors, 2- inhibition of phosphodiesterase, 3 - mobilization of intracellular calcium, and 4 - inhibition of  $\gamma$ -aminobutyric acid transmission. The latter three mechanisms do not exert a significant effect until serum concentrations rise above 25  $\mu$ g/ml. (Gurley, Steelman & Thomas, 2014).

It is the first mechanism, the antagonism of the adenosine receptors, where caffeine exerts its stimulant effects. In the brain, this includes mood enhancement, wakefulness, insomnia, anxiety, and tremors. Caffeine also increases secretion of epinephrine (Heckman et al., 2010) and other neurotransmitters (e.g., dopamine, norepinephrine, and serotonin) (Gurley et al., 2014). Chronic caffeine use causes an upregulation of adenosine receptors in the brain which results in tolerance to its effects (Broderick & Benjamin, 2004).

Throughout the rest of the body, caffeine also exhibits a variety of effects. In the heart and vasculature, the adenosine receptor antagonism increases heart rate, coronary and peripheral vasoconstriction, and elevated blood pressure. (Gurley et al., 2014; Broderick & Benjamin, 2004). Caffeine can cause fluid and electrolyte imbalances through “mild diuresis via increased glomerular filtration and enhanced sodium and water excretion” (Gurley et al., 2014). Caffeine also elevates blood glucose concentrations when consumed alongside a glucose/carbohydrate load (Whitehead & White, 2013).

Caffeine's metabolism occurs primarily in the liver through catalyzation of the CYP 1A2 enzyme. This same enzyme is also involved in the direct metabolism of a number of psychiatric medications. Those substrates include amitriptyline, clomipramine, clozapine, duloxetine, haloperidol, imipramine, melatonin (Papagiannidou, Skene, & Ioannides, 2014), olanzapine, and propranolol (Flockhart, 2007). Fluvoxamine is a potent inhibitor of CYP 1A2. Inducers of CYP 1A2 include carbamazepine, insulin, and modafinil (Flockhart, 2007).

Lithium levels can be affected by the effect of caffeine on renal tubule blood flow. (Broderick et al., 2005; Carillo & Benitz, 2000). The anti-diabetes drug metformin increases the plasma concentration of caffeine (Mohiuddin, Azam, Amran & Hossain, 2009). Caffeine is to be used with caution when combined with stimulants such as those used to treat attention disorders and depression due to the additive effect on the central nervous system (Vanattou-Saïfoudine, McNamara & Harkin, 2012). Caffeine has been found to lower seizure threshold and diminish the protective effects of carbamazepine, phenobarbital, phenytoin, valproate, and topiramate. (Chrościńska-Krawczyk, M., Jargiełło-Baszak, M., Walek, M., Tylus, B. & Czuczwar, S. J., 2011). Tobacco smoking is known to induce CYP 1A2 through activation of the aromatic hydrocarbon receptor. Recently marijuana was found to have the same action (Anderson & Chan, 2016).

Guarana. Guarana is contained in four of the six energy drinks (Appendix A.1). It is extracted from the seeds of the *Paullinia cupana* plant originally found in the Amazon basin in Brazil. Guarana contains caffeine as 2.7% -5.8% of the dry weight, as well as the other xanthine alkaloids theobromine and theophylline in lower concentrations than caf-

feine. (Scholey & Haskell, 2008; Heckman et al., 2010; Meurer-Grimes, Berkov, & Beck, 1998). “A majority of information related to adverse effects of guarana is based in theory upon the adverse effect profile of caffeine” (Natural Medicine database (NMD)) however its psychoactive properties may also be due to other components such as saponins, tannins, catechin, and epicatechin (Haskell, Kennedy, Wesnes, Milne, & Scholey, 2007; Scholey & Haskell, 2008).

Guarana has GRAS status as a permitted food additive as a natural flavoring and is, therefore, an allowed ingredient in energy drinks (FDA Flavoring Agents and Related Substances (Guarana), 2017). Guarana has no established dosing range. “There are no available, reliable human trials demonstrating safety or efficacy from a particular dose of guarana” (NMD).

Known interactions with psychiatric medications follow those of caffeine. However, Scholey and Haskell (2008) caution, “...it is unclear to what extent the various components of guarana might constitute an ‘active principle.’ Certainly, it appears that caffeine alone cannot account for the behavioral effects of guarana.”

Ginseng (panax ginseng). Three of the six energy drinks contain panax ginseng (Appendix A.1). Ginseng is a slow-growing deciduous plant that grows in Korea, northeastern China, and far-eastern Siberia (NMD). Its medicinal use in many Asian countries dates back thousands of years. “The traditional uses of ginseng primarily revolve around promoting digestive system functions, improving nutrition, and calming agitation; the modern applications in Asia are particularly aimed at preventing and treating cardiovascular diseases and problems of aging, including diabetes. By contrast,

ginseng is often currently described in the West as an energizing agent...” (Subhuti, n.d.). Of its 13 different species, the root of the panax ginseng is the one most frequently used in energy drinks.

There is no standard dosing guideline for ginseng. In Asia, doses of 3-9 g/day are used (Subhuti, n.d.). Doses up to 9 g daily over 12 weeks have been studied in relation to cognitive performance in patients with Alzheimer’s disease. However, a systematic review concluded, “the evidence for ginseng as a treatment of Alzheimer’s Disease is scarce and inconclusive.” (Lee, Yang, Kim, & Ernst, 2009). As described in Norelli and Xu’s (2015) report, high dose and longer duration of use were connected to new onset psychosis in two patients with no psychiatric history. The mania resolved upon the discontinuation of the ginseng. For use within regular guidelines, it is generally well-tolerated with insomnia, diarrhea, and abdominal pain reported as the most common side effects (Malati et al., 2012).

Panax ginseng was submitted to the FDA in 1999 for GRAS status for use as an ingredient in a non-carbonated fruit beverage or tea (FDA, 2000, April 10). Within four months of submission, the filing company withdrew their request, so the FDA ceased to evaluate the request any further. The original notice was assigned GRAS notice number GEN 000036 (FDA, 2000, April 26).

Ginseng's absorption through the gastrointestinal tract is a result of the breakdown of ginsenosides by the intestinal microflora. A study by Liu et al. (2006), evaluated the influence of ginsenosides on P450 CYP liver enzymes and found that “naturally occurring ginsenosides exhibited no inhibition or weak inhibition against human CYP 3A4, 2D6, 2C9, 2A6, or 1A2 activities...” However, they also found that once the ginsenosides

were metabolized in the intestine, three of those metabolites had “moderate inhibition against CYP 2C9 activity” and two of those three also “exhibited potent competitive inhibition against CYP 3A4 activity”. The variation in ginseng efficacy is posited to be a result of the differences in ginseng product ingested, genetic differences in metabolism via P450, and each individual's microflora (Lee et al., 2009; Liu et al., 2006).

According to the *Natural Medicines* database (NMD), ginseng should be used with caution in combination with CYP 3A4 substrates such as fluoxetine (Prozac) and propranolol (Inderal).

Natural Medicines database also states further study is warranted for potential interactions with MAOI's due to case reports of insomnia, headache, tremors, and hypomania associated with phenelzine (Nardil) (Jones & Runikis, 1987; Shader & Greenblatt, 1985; Shader & Greenblatt, 1988).

In regards to CYP 2D6 substrates, NMD cites contradictory research as reason to use caution with ginseng in combination with amitriptyline (Elavil), clozapine (Clozaril), desipramine (Norpramin), donepezil (Aricept), fluoxetine (Prozac), olanzapine (Zyprexa), and trazodone (Desyrel).

There are also concerns about ginseng's effect on the electrocardiogram QTc interval. Studies of panax ginseng ingestion have found significant changes in QTc interval 2 hours post ingestion (Fletcher, Lacey, & Shah, 2014; Caron et al., 2002). When taken in conjunction with psychotropic medications that are also known to prolong the QTc interval, the risk of a serious adverse event increases. In their 2012 article, Washington, Brahm, and Kissack published a review of psychotropic medications that increase the risk of QTc prolongation. Antidepressants found to increase QTc interval

included the tricyclics, particularly amitriptyline, but also desipramine and nortriptyline. When used in supra-therapeutic doses, as is often seen in psychiatric practice, all selective serotonin reuptake inhibitors (SSRI)'s have been reported to prolong the QTc interval. Select antipsychotics are also associated with QTc prolongation. Of the first-generation antipsychotics, thioridazine, chlorpromazine, and haloperidol have documented cardiac risk. Of the atypical antipsychotics, long-term use of ziprasidone has been associated with QTc prolongation more often than with risperidone, olanzapine or quetiapine. Clozapine also has cardiac side effects (including QTc prolongation) that are dose-dependent. (Alvarez & Pahissa, 2010).

Taurine (2-aminoethane sulfonic acid). Taurine is an ingredient in all six of the energy drinks (Appendix A.1). Rockstar® is the only one of the six to declare the amount of taurine in their drink, listing 1,000 mg per serving in their two serving (16 oz) can. Mean daily consumption from regular food sources is estimated at 20-200 mg/day (Stapleton, Charles, Redmond & Boucher-Hayes, 1997), and up to 400 mg/day (Aguilar et., 2009). It received GRAS approval from the FDA in 2015 “for use as an ingredient in enhanced water beverages at a concentration of 45 parts per million (0.0045%)” (FDA, 2015). This equates to about 16 mg/12 oz. (Triebel, Sproll, Reusch, Godelmann & Lachenmeier, 2007). Triebel et al. (2007) analysis of taurine content in 80 energy drinks showed a minimum concentration of 88 mg/L and maximum 5435 mg/L, resulting in an average concentration of 3180 mg/L (735 mg/8 oz).

Taurine is the most abundant free amino acid in the body. It is important for “membrane stabilization, detoxification, antioxidation, osmoregulation, maintenance of

calcium homeostasis, and stimulation of glycolysis and glycogenesis” (Stapleton et al., 1997). Since it is essential for normal development of the brain and retina, but only obtainable through consumption of meat, dairy products, poultry, fish, and breast milk, it is added to infant formula for those babies wholly reliant on formula (Heckman et al., 2010; Stapleton et al., 1997). In the body, high levels are found in the heart, brain, liver, and granulocytes (Stapleton et al., 1997). Also, about  $\frac{1}{4}$ <sup>th</sup> of bile acids are conjugated with taurine (Sturman, Hepner, Hofmann & Thomas, 1975). It exits the body unchanged in the urine, indicating “that exogenous taurine rapidly equilibrates with endogenous body pools and that any excess is rapidly eliminated by the kidneys” (Stapleton et al., 1997; EFSA, 2009; Munro & Renwick, 2006). It is due to this action of equilibrium that Munro and Renwick, in the 5<sup>th</sup> Workshop on the Assessment of Adequate Intake of Dietary Amino Acids: General Discussion 2 (2006), stated: “high dietary intakes of taurine should not be a toxicological problem.” Heckman et al. (2010) cite a number of studies conducted on various doses ranging from 375-8000 mg/d, as well as studies looking into the safety of taurine in humans, showing no adverse effects.

However, Heckman et al. (2010) also caution against blanket acceptance of taurine's safety in energy drinks citing a lack of research on the specific effects of large quantities of taurine in combination with the other ingredients. In fact, two published case reports describe acute renal failure specifically due to the taurine in consumed energy drinks. (Schöffl, Kothmann, Schöffl, Rupprecht, & Rupprecht, 2011; Greene, Oman, & Lefler, 2014).

Due to its clearance through the kidneys, “Taurine is thought to have diuretic properties. Theoretically, due to these potential diuretic effects, taurine might reduce

excretion and increase levels of lithium. The dose of lithium might need to be decreased” (NMD).

B Vitamins. The eight water-soluble B vitamins each play an essential role in brain function, individually as well as in concert with each other. They cross the blood-brain barrier where their concentrations are kept high through tightly regulated mechanisms. Daily turnover ranges from 8% - 100% per day. Being water-soluble, excesses are excreted in the urine. Therefore they are typically safe at doses much higher than the RDA, with the exceptions of B9 (folic acid), B3 (niacin), and B6 (pyroxidine hydrochloride) (Kennedy, 2016).

Six of the eight B vitamins are found in a variety of combinations in each of the above six drinks, although none contain all eight. Common to all six are Vitamin B6 (pyridoxine) and Vitamin B12 (cyanocobalamin). Absent from all six are B7 (biotin) and B1 (thiamine). Five of the six include B3 (niacin); four include B2 (riboflavin) and three B5 (pantothenic acid), and only one of the six includes B9 (folic acid) (Appendix A.1).

B6 (pyroxidine hydrochloride). In the brain, B6 is a “rate limiting cofactor in the synthesis of neurotransmitters such as dopamine, serotonin,  $\gamma$ -aminobutyric acid (GABA), noradrenaline and the hormone melatonin. The synthesis of these neurotransmitters is differentially sensitive to Vitamin B6 levels, with even mild deficiency resulting in preferential down-regulation of GABA and serotonin synthesis, leading to the removal of inhibition of neural activity by GABA and disordered sleep, behaviour and cardiovascular function and a loss of hypothalamus-pituitary control of hormone excretion” (Kennedy, 2016). It is also a necessary cofactor in the folate cycle,

plays a role in glucose regulation, and is connected to inflammatory processes such as those seen with dementia and cognitive decline (Kennedy, 2016). High doses can cause reversible sensory neuropathy, gradual progressive sensory ataxia, rosacea fulminans, and photosensitivity (Rogovik, Vohra, & Glodman, 2010).

Table 2 Vitamin B6 (*pyroxidine hydrochloride*)

Recommended Daily Allowance <sup>a</sup>	19-50 years old	1.3 mg/day
Females	50+ years old	1.7 mg/day
Males	14-50 years old	1.3 mg/day
	50+ years old	1.7 mg/day
Daily Value <sup>b</sup>	2 mg/day	
Tolerable Upper Limit <sup>c</sup>	100 mg/day due to sensory neuropathy occurring from high oral intake of supplemental doses (specifically > 1 g/day)	
% Daily Value (DV): Vitamin B6 ( <i>pyroxidine hydrochloride</i> )		
Amp®	20%	
Monster®	200%	
NOS®	200%	
Red Bull®	250%	
Rockstar®	100%	
5-Hour Energy®	2000% (40mg)	
Interactions: Vitamin B6 ( <i>pyroxidine hydrochloride</i> )		
Moderate <sup>d</sup>	Increased hypotension with antihypertensive medications (i.e., propranolol, used for some patients for anxiety). <sup>d</sup>	
Minor <sup>d</sup>	Pyroxidine enhances the metabolism of levodopa, reducing its anti-parkinsonism effects. However, this interaction does not occur when carbidopa is used concurrently with levodopa (Sinemet). Therefore, it is not likely to be a problem for most people.” <sup>d</sup>	

Table 2 Continued

Note. <sup>a</sup> adapted from Vitamin B6. (1998). *Recommended Dietary Allowances: 10th Edition*. National Research Council. Washington, DC: The National Academies Press. doi.org/10.17226/1349.

<sup>b</sup> adapted from U.S. Food and Drug Administration. Center for Food Safety and Applied Nutrition [CFSAN]. (2013, January). *Guidance for Industry: A Food Labeling Guide (14. Appendix F: Calculate the Percent Daily Value for the Appropriate Nutrients)*. Retrieved from <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm064928.htm>

<sup>c</sup> adapted from *Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels, Vitamins*. (n.d.). Food and Nutrition Board, Institute of Medicine, The National Academies Press. Retrieved from [http://www.nationalacademies.org/hmd/~media/Files/Activity%20Files/Nutrition/DRI-Tables/4\\_%20UL%20Values\\_Vitamins%20and%20Elements.pdf?la=en](http://www.nationalacademies.org/hmd/~media/Files/Activity%20Files/Nutrition/DRI-Tables/4_%20UL%20Values_Vitamins%20and%20Elements.pdf?la=en)

<sup>d</sup> Vitamin B6 Monograph. In: Jellin, J. M., Gregory, P. J., ... et al. *Natural Medicines*. Retrieved from [www.naturalmedicines.com](http://www.naturalmedicines.com).

B12 (cyanocobalamin). B12 is a cofactor necessary for many metabolic processes including red blood cell formation, DNA synthesis, and fat and protein metabolism. It is essential for folate utilization, with a deficiency resulting in a functional folate deficiency. Also with folate, it plays a critical role in neuronal myelination, as well as the production of an essential cofactor involved in the production of monoamine neurotransmitters (serotonin, melatonin, dopamine, noradrenaline, and adrenaline) (Kennedy, 2016). Ingesting large doses of B12 without causing adverse effect is possible due to the decreased absorption once the capacity of intrinsic factor is exceeded (Office of Dietary Supplements [ODS], 2016).

Table 3 Vitamin B12 (*cyanocobalamin*)

Recommended Daily Allowance <sup>a</sup>		
Females and males	14+ years old	2.4 µg/day
Daily Value <sup>b</sup>	6 µg/day	
Tolerable Upper Limit	“No adverse effects have been associated with excess B12 intake from food or supplements in healthy individuals.” <sup>a</sup>	

Table 3 Continued

% Daily Value (DV) : Vitamin B12 (cyanocobalamin)	20%	
Amp®	200%	
Monster®	200%	
NOS®	80%	
Red Bull®	100%	
Rockstar®	8333%	(500mcg)
5-Hour Energy®		

Interactions: Vitamin B12 (cyanocobalamin)  
No interactions with psychotropic medications were noted in the Natural Medicines Database.<sup>d</sup>

Note. <sup>a</sup> adapted from Vitamin 12. (1998). *Recommended Dietary Allowances: 10th Edition*. National Research Council. Washington, DC: The National Academies Press. doi.org/10.17226/1349.

Table 3 Continued

<sup>b</sup> adapted from U.S. Food and Drug Administration. Center for Food Safety and Applied Nutrition [CFSAN]. (2013, January). *Guidance for Industry: A Food Labeling Guide (14. Appendix F: Calculate the Percent Daily Value for the Appropriate Nutrients)*. Retrieved from <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm064928.htm>

<sup>c</sup> adapted from *Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels, Vitamins*. (n.d.). Food and Nutrition Board, Institute of Medicine, The National Academies Press. Retrieved from [http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRI-Tables/4\\_%20UL%20Values\\_Vitamins%20and%20Elements.pdf?la=en](http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRI-Tables/4_%20UL%20Values_Vitamins%20and%20Elements.pdf?la=en)

<sup>d</sup> Vitamin B12 Monograph. In: Jellin, J. M., Gregory, P. J., ... et al. Natural Medicines. Retrieved from [www.naturalmedicines.com](http://www.naturalmedicines.com).

“Approximately 56% of a 1 mcg oral dose of vitamin B12 is absorbed, but absorption decreases drastically when the capacity of intrinsic factor is exceeded (at 1–2 mcg of vitamin B12)” (ODS, 2016). Cyanocobalamin is a common synthetic form of vitamin B12 that is used in most supplements (Watanabe, 2007).

B9 (folic acid). Folic acid aids in protein metabolism, neural tube formation, neuronal myelination, promotes red blood cell formation, and may play a role in reducing

coronary heart disease risk by controlling homocysteine levels (Bellows & Moore, 2012). It is complementary to B12 in that if B12 is deficient, folate is not able to undergo necessary enzymatic cycles which results in a functional folate deficiency as well. Also, as with B12, the functioning of the folate cycle is necessary for the production of an essential cofactor involved in the production of monoamine neurotransmitters (serotonin, melatonin, dopamine, noradrenaline, and adrenaline) (Kennedy, 2016).

Patients who took folic acid in the form of l-methylfolate (Deplin®), in conjunction with conventional antidepressants, “achieved statistically significant improvements in self-reported depression symptoms and functioning and greater satisfaction with their medication treatment” (Shelton, Manning, Barrentine & Tipton, 2013). Folic acid was found to reduce affective morbidity in a group of patients treated with lithium (Coppens, Chaudhry, & Swade, 1986). Behzadi, Omrani, Chalian, Asadi, & Ghadiri (2009) found folate “an effective adjuvant to sodium valproate in the treatment of the acute phase of mania in patients with bipolar disorder.”

Folic acid has a designated Tolerable Upper Limit (TUL) due to the potential to mask underlying B12 deficiency. Doses up to 5mg/day have been related to abdominal cramps, diarrhea, and rash. Doses above 15 mg/day “can cause altered sleep patterns, irritability, confusion, exacerbation of seizure frequency, nausea and flatulence; precipitate or exacerbate neuropathy in people deficient in vitamin B12; and rarely cause allergic reactions (rash, erythema, itching, malaise, and bronchospasm). Higher rates of prostate and breast cancer have also been shown to occur with high dose folate intake. (Rogovik et al., 2010).

Table 4 Vitamin B9 (*folic acid*)

Recommended Daily Allowance <sup>a</sup>		
Females and males	14+ years old	400 µg/day
Daily Value <sup>b</sup>		
	400 µg/day	
Tolerable Upper Limit <sup>c</sup>		
	1,000 µg/day	
	due to potentially obscuring or masking Vitamin B12 deficiency and subsequent neurological complications. “The UL for folate applies to synthetic forms obtained from supplements and/or fortified foods.” <sup>a</sup>	
% Daily Value: Vitamin B9 ( <i>folic acid</i> )		
Amp®	0%	
Monster®	0%	
NOS®	0%	
Red Bull®	0%	
Rockstar®	0%	
5-Hour Energy®	100%	(400 mcg)
Interactions: Vitamin B9 ( <i>folic acid</i> )		
Moderate <sup>d</sup>	While specific drug-drug interactions with psychiatric medications are not indicated, carbamazepine can reduce serum folate levels which “might contribute to mild, asymptomatic reductions in nerve conduction velocities, and mental changes seen with carbamazepine.” <sup>d</sup>	
	Valproate may also reduce folate levels in some people, although symptomatic deficiency has not been reported. <sup>d</sup>	

Note. <sup>a</sup> adapted from Folate. (1998). *Recommended Dietary Allowances: 10th Edition*. National Research Council. Washington, DC: The National Academies Press. doi.org/10.17226/1349.

<sup>b</sup> adapted from U.S. Food and Drug Administration. Center for Food Safety and Applied Nutrition [CFSAN]. (2013, January). *Guidance for Industry: A Food Labeling Guide (14. Appendix F: Calculate the Percent Daily Value for the Appropriate Nutrients)*. Retrieved from <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm064928.htm>

<sup>c</sup> adapted from *Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels, Vitamins*. (n.d.). Food and Nutrition Board, Institute of Medicine, The National Academies Press. Retrieved from

Table 4 Continued

[http://www.nationalacademies.org/hmd/~media/Files/Activity%20Files/Nutrition/DRI-Tables/4\\_%20UL%20Values\\_Vitamins%20and%20Elements.pdf?la=en](http://www.nationalacademies.org/hmd/~media/Files/Activity%20Files/Nutrition/DRI-Tables/4_%20UL%20Values_Vitamins%20and%20Elements.pdf?la=en)

<sup>d</sup> Folic acid monograph. In: Jellin, J. M., Gregory, P. J., ... et al. Natural Medicines. Retrieved from [www.naturalmedicines.com](http://www.naturalmedicines.com).

**B2 (riboflavin).** Riboflavin is an essential component of two coenzymes which both “play major roles in energy production; cellular function, growth, and development; and metabolism of fats, drugs, and steroids” (ODS, 2016). It is also needed for the conversion of tryptophan to niacin and as well as the conversion of B6. “Riboflavin intake many times higher than the Recommended Dietary Allowance (RDA) is apparently without demonstrable toxicity. Nevertheless, the photosensitizing properties of riboflavin raise the possibility of some potential risks. According to various secondary sources, other possible reactions to very high doses include itching, numbness, burning or prickling sensations, and yellow discoloration of the urine” (NMD).

Table 5 Vitamin B2 (*riboflavin*)

Recommended Daily Allowance <sup>a</sup>		
Females	19+ years old	1.1 mg/day
Males	14+ years old	1.3 mg/day
Daily Value <sup>b</sup>	1.7 mg/day	
Tolerable Upper Limit <sup>c</sup>	“No adverse effects associated with riboflavin consumption from food or supplements have been reported.” <sup>a</sup>	
% Daily Value: Vitamin B2 ( <i>riboflavin</i> )		
Amp®	40%	
NOS®	0%	
Monster®	200%	
Red Bull®	0%	
Rockstar®	200%	

Table 5 Continued

5-Hour Energy®	0%
Interactions: Vitamin B2 ( <i>riboflavin</i> )	
Mild <sup>d</sup>	<p>Anticholinergics decrease rate of supplemental riboflavin absorption, but increase total amount absorbed due to slowed gut motility which leaves the vitamin available longer.<sup>d</sup></p> <p>“Tricyclic antidepressants have structural similarities to riboflavin and can interfere with its conversion” to its active form (Pinto, Huang, &amp; Rivlin, 1981) although “Since these doses are higher than those used therapeutically in humans, it is unlikely that the effect is clinically significant or that supplements are necessary.”<sup>d</sup></p>

Note. <sup>a</sup> adapted from Riboflavin. (1998). *Recommended Dietary Allowances: 10th Edition*. National Research Council. Washington, DC: The National Academies Press. doi.org/10.17226/1349.

<sup>b</sup> adapted from U.S. Food and Drug Administration. Center for Food Safety and Applied Nutrition [CFSAN]. (2013, January). *Guidance for Industry: A Food Labeling Guide (14. Appendix F: Calculate the Percent Daily Value for the Appropriate Nutrients)*. Retrieved from <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm064928.htm>

<sup>c</sup> adapted from *Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels, Vitamins*. (n.d.). Food and Nutrition Board, Institute of Medicine, The National Academies Press. Retrieved from [http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRI-Tables/4\\_%20UL%20Values\\_Vitamins%20and%20Elements.pdf?la=en](http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRI-Tables/4_%20UL%20Values_Vitamins%20and%20Elements.pdf?la=en)

<sup>d</sup> Riboflavin monograph. In: Jellin, J. M., Gregory, P. J., ... et al. *Natural Medicines*. Retrieved from [www.naturalmedicines.com](http://www.naturalmedicines.com).

**B3 (niacin)**. Niacin functions as a coenzyme in energy metabolism, fat synthesis, and fat breakdown. In addition, some dietary tryptophan is converted to niacin in the body.”(NMD). In the brain, one of the niacin receptors (NIACR1) has “been shown to be up-regulated in the substantia nigra of Parkinson's disease sufferers (a group that has low niacin levels generally) with levels correlating with poorer sleep architecture in this

group.” The same NIACR1 receptors have been shown to be down-regulated in the anterior cingulate cortex of people with schizophrenia (Kennedy, 2016).

Table 6 Vitamin B3 (*niacin*)

Recommended Daily Allowance <sup>a</sup>		
Females	14+ years old	14 mg/day
Males	14+ years old	16 mg/day
Daily Value <sup>b</sup>		20 mg/day
Tolerable Upper Limit <sup>c</sup>		30mg/day - due to flushing reaction with itching on the face, arms, and chest, increased intracranial blood flow, and headache
% Daily Value: Vitamin B3 ( <i>niacin</i> )		
Amp®	20%	
NOS®	0%	
Monster®	200%	
Red Bull®	100%	
Rockstar®	100%	
5-Hour Energy®	150%	(30 mg)
Interactions: Vitamin B3 ( <i>niacin</i> )		
		Doses of niacin above 1.5 g/day can “impair glucose tolerance in a dose-dependent manner, probably by causing or aggravating insulin resistance and increasing hepatic production of glucose.” <sup>d</sup>
Moderate <sup>d</sup>		<p>“Plasma levels of carbamazepine were increased in two children given high-dose niacinamide, 60 to 80 mg/kg/day. This might be due to inhibition of the cytochrome P450 enzymes involved in carbamazepine metabolism. There is not enough data to determine the clinical significance of this interaction.”<sup>d</sup></p> <p>“Clonidine seems to inhibit niacin-induced flushing; however, the combination might also exacerbate orthostatic hypotension and should be used cautiously in people prone to this condition.”<sup>d</sup></p> <p>Moderate depletion: levodopa/carbidopa - “Dopa decarboxylase inhibitors such as carbidopa inhibit an</p>

Table 6 Continued

	<p>enzyme involved in conversion of tryptophan to niacin. Evidence of subclinical niacin deficiency was found in people treated with levodopa/carbidopa, but pellagra has not been reported.”<sup>d</sup></p> <p>“Case reports describe symptomatic niacin deficiency in people taking valproic acid alone or in combination with other anticonvulsants; however, the mechanism is not known.”<sup>d</sup></p>
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*Note.* <sup>a</sup> adapted from Niacin. (1998). *Recommended Dietary Allowances: 10th Edition*. National Research Council. Washington, DC: The National Academies Press. doi.org/10.17226/1349.

<sup>b</sup> adapted from U.S. Food and Drug Administration. Center for Food Safety and Applied Nutrition [CFSAN]. (2013, January). *Guidance for Industry: A Food Labeling Guide (14. Appendix F: Calculate the Percent Daily Value for the Appropriate Nutrients)*. Retrieved from <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm064928.htm>

<sup>c</sup> adapted from *Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels, Vitamins*. (n.d.). Food and Nutrition Board, Institute of Medicine, The National Academies Press. Retrieved from [http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRI-Tables/4\\_%20UL%20Values\\_Vitamins%20and%20Elements.pdf?la=en](http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRI-Tables/4_%20UL%20Values_Vitamins%20and%20Elements.pdf?la=en)

<sup>d</sup> Niacin monograph. In: Jellin, J. M., Gregory, P. J., ... et al. *Natural Medicines*. Retrieved from [www.naturalmedicines.com](http://www.naturalmedicines.com).

B5 (pantothenic acid). As a substrate for the synthesis of coenzyme A (CoA),

“Pantothenic acid is required for the metabolism of carbohydrates, proteins, and fats, as well as for the synthesis of hormones and cholesterol” (NMD). “...Via CoA, it is also involved in the synthesis of multiple neurotransmitters and steroid hormones” (Kennedy, 2016). Amounts up to 10 g can be consumed without significant adverse effects.

Table 7 Vitamin B5 (*pantothenic acid*)

Adequate intake (AI)	
Females and males	5 mg/day - (“Daily adequate intake (AI) of pantothenic acid levels have been established by the Food and Nutrition Board of the U.S. Institute of Medicine, based on estimated dietary intakes in healthy

Table 7 Continued

	populations. A recommended dietary allowance (RDA) is lacking, due to insufficient available scientific evidence.” <sup>d</sup>
Daily value <sup>b</sup>	10 mg
Tolerable Upper Limit <sup>c</sup>	Currently, no sufficient scientific evidence on which to base a Tolerable Upper Intake Level for pantothenic acid. <sup>d</sup>
% Daily Value: Vitamin B5( <i>pantothenic acid</i> )	
Amp®	20%
NOS®	0%
Monster®	0%
Red Bull®	50%
Rockstar®	100%
5-Hour Energy®	0%
Interactions: Vitamin B5 ( <i>pantothenic acid</i> )	
No negative interactions with psychotropic medications were noted in the NMD. Of note, supplementation for those patients experiencing side effects from valproic acid (nausea, tremors, liver failure) “has been suggested as beneficial in modulating such symptoms” (Zempleni et al., ch 9).	

Note. <sup>a</sup> adapted from Pantothenic acid monograph. (1998). *Recommended Dietary Allowances: 10th Edition*. National Research Council. Washington, DC: The National Academies Press. doi.org/10.17226/1349.

<sup>b</sup> adapted from U.S. Food and Drug Administration. Center for Food Safety and Applied Nutrition [CFSAN]. (2013, January). *Guidance for Industry: A Food Labeling Guide (14. Appendix F: Calculate the Percent Daily Value for the Appropriate Nutrients)*. Retrieved from <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm064928.htm>

<sup>c</sup> adapted from *Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels, Vitamins*. (n.d.). Food and Nutrition Board, Institute of Medicine, The National Academies Press. Retrieved from [http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRI-Tables/4\\_%20UL%20Values\\_Vitamins%20and%20Elements.pdf?la=en](http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRI-Tables/4_%20UL%20Values_Vitamins%20and%20Elements.pdf?la=en)

<sup>d</sup> Pantothenic acid monograph. In: Jellin, J. M., Gregory, P. J., ... et al. *Natural Medicines*. Retrieved from [www.naturalmedicines.com](http://www.naturalmedicines.com).

Each energy drink's remaining ingredients are comprised of various combinations of glucuronolactone, inositol, *L*-carnitine, *L*-tartrate, *L*-theanine, *L*-phenylalanine, *n*-acetyl *L*-tyrosine, citicoline, malic acid, and milk thistle extract.

Glucuronolactone. Glucuronolactone is in three of the six energy drinks (Appendix A.1). Along with being an additive, it occurs naturally in the body. It is formed from glucose in the liver and is a component of all connective tissue. It is readily absorbed when ingested, hydrolyzed, then excreted in the urine as glucuronic acid (McLellan & Lieberman, 2012). It has shown hepatoprotective effects in rats (Chen, Chiu, Tseng, Yang & Chen, 2015) and is believed to aid in detoxification, freeing hormones and other chemicals, and the biosynthesis of vitamin C. It is added to energy drinks to help prevent other substances from depleting glycogen supplies in the muscles (Yunusa & Ahmad, 2011) and lessened fatigue (in rats) following hard exercise (Tamura, S., Tsutsumi, S., Ito, H., Nakai, K. & Masuda, M., 1968; Tamura et al., 1966). Higgins, Tuttle, and Higgins (2010) states “unfortunately, little research has been done in humans, and the current body of knowledge on this substance is scant. Therefore, conclusions on whether this compound (as supplementation) is harmful or beneficial cannot be made”. Specific to energy drinks, the 2003 European Food Safety Authority (EFSA) committee “was unable to conclude that the safety-in-use of these constituents in the concentration ranges reported for “energy” drinks had been adequately established. Further studies would be required to establish safe levels for daily intake of... glucuronolactone.” McLellan and Lieberman (2012) found “no experimental evidence showing that the addition of glucuronolactone to

a caffeinated energy drink will cause improvements in physical or cognitive performance than can be attributed to the effects of caffeine alone.”

No interactions with psychotropic medications were found in the Natural Medicine Database.

Inositol. Inositol is present in two of the energy drinks (Appendix A.1). Sometimes referred to as Vitamin B8, inositol is an isomer of glucose that occurs naturally, but can also be extracted from corn kernels (FDA Inositol, 2017). It “is a key intermediate of the phosphatidyl-inositol (PI) cycle, a second-messenger system which is linked to several noradrenergic, serotonergic and cholinergic receptors” (Benjamin, Agam, Levine, Bersudsky, Kofman, & Belmaker, 1995; Camfield, Sarris, and Berk, 2011). It has been studied as a potential treatment for a number of psychiatric disorders, and has been suggested as beneficial for depression, PMDD (premenstrual dysphoric disorder), panic disorder and obsessive-compulsive disorder (Levine, 1997; Mukai, Kishi, Matsuda, & Iwata, 2014; NMD). However, a systematic review by Ravindran & Silva (2013) summarized there was “insufficient evidence to recommend inositol augmentation in either depressive or anxiety conditions.”

Inositol is generally well tolerated although it can cause nausea, tiredness, headache, and dizziness. (Palatnik, 2001; Allan, Kavanagh, Herd & Savin, 2004) On its can label, Rockstar® declares 25 mg per serving (50 mg per 16 oz can) which is negligible compared to the 18g utilized for panic disorder and OCD, and the 6g dosing for lithium-related psoriasis (NMD).

Inositol is affirmed as GRAS (FDA Inositol, 2017) for use in food “,with no limitations other than current good manufacturing practice.”

There are no known interactions with inositol and any medications (NMD). Interestingly, “Supplemental inositol seems to help psoriasis that is made worse or triggered by lithium. The mechanism is unknown, but lithium seems to cause a reduction of inositol in both the brain and other tissues. Supplementation with inositol does not seem to adversely affect the efficacy of lithium for bipolar disorder” (NMD; Allan et al., 2004).

*L-carnitine*. *L-carnitine* is in 2 of the six energy drinks (Appendix A.1). It is an amino acid derived from meat and meat products, as well as seafood and dairy products (Williams, 2007). It is made predominantly by the liver and kidneys via synthesis of lysine and methionine (Steiber, Kerner, and Hoppel, 2004; Higgins et al., 2010). More than 90% is stored in the skeletal muscle (Bain et al., 2006). “The main function of *L-carnitine* is to transfer long-chain fatty acids in the form of their acyl-carnitine esters across the inner mitochondrial membrane before beta-oxidation” (Vidal-Casariago et al., 2013) which allows the body to turn fat into energy (Goa & Brogden, 1987). It also facilitates the removal of metabolic waste, thereby preventing acidosis (Carnitor®, 2006).

As a supplement, *L-carnitine* has not been categorized as GRAS by the FDA as a nutrient and/or dietary supplement (FDA Substances Generally Recognized As Safe, 2017; ODS, 2017). There is, however, an FDA approved prescription (Carnitor®) indicated for the treatment of primary systemic carnitine deficiency, as well as for patients with an inborn error of metabolism resulting in a secondary carnitine deficiency. Particu-

lar to psychiatry, another of its uses is to treat severe valproic acid-induced hepatotoxicity, especially in patients treated for overdose or accidental ingestion of valproic acid. (Perrott, 2010). Dosing guidelines are 1-3 g/day in divided doses. Side effects are generally mild and include nausea, vomiting, abdominal cramps, diarrhea and a “fishy” body odor. Seizures have also been reported in patients with or without pre-existing seizure activity, and those with a pre-existing seizure disorder had an increase in seizure frequency and/or severity (Carnitor®, 2006). Once its serum concentrations are stabilized, any excess is excreted predominately via the kidney (Carnitor®, 2006; ODS, 2017).

Although *L*-carnitine does not have any direct interactions with psychiatric medications, caution should still be applied due to its effect on both triiodothyronine (T3) and thyroxine (T4) (Benvenga, Amato, Calvani, & Trimarchi, 2004). “*L*-carnitine appears to act as a peripheral thyroid hormone antagonist by inhibiting entry of thyroid hormone into the nucleus of cells...Theoretically, taking *L*-carnitine might decrease the effectiveness of thyroid hormone replacement” (NMD). This could be of concern for those patients taking lithium due to its own potential impact on the thyroid.

*L*-tartrate. *L*-tartrate is in one of the energy drinks (Appendix A.1). Tartaric acid is an organic acid found primarily in grapes and tamarinds. It is one of the main acids found in wine and is added to other foods to produce a sour taste. It is metabolized by bacteria primarily in the large intestine. About 15-20% is excreted in the urine unchanged and is thought to play a role in inhibiting kidney stone formation. Through its inhibiting the production of malic acid, it is a muscle toxin in high doses (12 g.), which can lead to paralysis and death (L-tartaric acid, n.d)

*L*-tartrate has GRAS status when “used in food with no limitation other than current good manufacturing practice” (FDA Tartaric acid, 2017).

There are no listed interactions for *L*-tartrate (alpha hydroxy acids) with prescribed psychotropic medications in the NMD.

*L*-theanine. *L*-theanine is also in only one of the six energy drinks (Appendix A.1). *L*-theanine is an amino acid found primarily in tea (*Camellia sinensis*) leaves, but can also be chemically synthesized (CFSAN, 2014). In animal studies *L*-theanine was found to absorb through the intestinal tract, reaching peak plasma levels around 50 minutes. It is hydrolyzed in the kidney into glutamic acid and ethylamine (Nathan, Lu, Gray, & Oliver, 2006) and eventually excreted in the urine (Scheid et al., 2012). It also crosses the blood-brain barrier, with concentrations showing a significant increase at 1 hour, reaching a maximum level after 5 hours, then gradually decreasing to baseline within 24 hours (Terashima, Takido, & Yokogoshi, 1999). Studies suggest it affects serotonin, dopamine, and  $\gamma$ -aminobutyric acid (GABA) levels (Wakabayashi, Numakawa, Ninomiya, Chiba, & Kunugi, 2012; Nathan et al., 2006) as well as antagonistically binds to 3 glutamate receptor subtypes (Kakuda, Nozawa, Sugimoto, & Niino, 2002). Camfield, Stough, Farrimond, and Scholey (2014) state that due to *L*-theanine's effect on GABA, “it could be argued that *L*-theanine might act as a mild anxiolytic, which is consistent with its traditional use as a relaxation-promoting agent.” There is also interest in its potential effects on cognition and attention as well as its antidepressant-like and antipsychotic-like effects (Dodd, Kennedy, Riby, & Haskell-Ramsay, 2015; Wakabayashi et al., 2012).

Both the naturally occurring and chemically synthesized forms of *L*-theanine have GRAS status at levels up to 250 mg per serving (CFSAN, 2014).

There are no listed interactions for *L*-theanine with prescribed psychotropic medications in the Natural Medicines Database (NMD).

Pertinent to this researcher's current study on energy drinks Haskell, Kennedy, Milne, Wesnes, and Scholey (2008) studied the combined effects of *L*-theanine with caffeine. They found *L*-theanine had very few neurocognitive effects when alone. They also found “evidence of some effects of caffeine when combined with *L*-theanine, not seen with either treatment in isolation.” This led them to suggest that “beverages containing *L*-theanine and caffeine may have a different pharmacological profile to those containing caffeine alone.” In further research on the combination of *L*-theanine and caffeine in humans, *L*-theanine was found to attenuate some of the effects of caffeine. Although it did not impact caffeine-caused jitteriness, alertness, or other aspects of mood (Rogers, Smith, Heatherley, & Pleydell-Pearce, 2008), *L*-theanine was found to have an antagonizing effect on caffeine-caused blood pressure elevations. (Dodd et al., 2015; Rogers et al., 2008). The *L*-theanine/caffeine combination has also been found to positively impact speed on several cognitive tasks (Haskell et al., 2008), improve performance accuracy (Kelly, Gomez-Ramirez, Montesi, & Foxe, 2008), improve speed and accuracy on an attention-switching task (Owen, Parnell, De Bruin, & Rycroft, 2008), and increase subjective alertness and reduce task-induced fatigue (Giesbrecht, Rycroft, Rowson, & De Bruin, 2010).

Haskell, Dodd, Wightman, and Kennedy (2013) reviewed studies assessing co-occurring caffeine and phytochemicals and pronounced a significantly less favorable rec-

ommendation of the *L*-theanine/caffeine combination. “The over-riding conclusion is that *L*-theanine (in isolation) impairs attention. Although positive outcomes have been indicated by those studies that have explored its effects in combination, the majority do not allow delineation of effects of this combination over and above those of caffeine alone.”

Dodd et al. (2015) more recently examined the effects of *L*-theanine and caffeine on cerebral blood flow and demonstrated that “caffeine and *L*-theanine, at doses equivalent to one or two cups of tea, are capable of modulating cerebral hemodynamics, cognitive performance, mood and autonomic measures...This supports previous findings of an interaction between these substances, despite lack of effects of *L*-theanine in isolation.”

Dodd et al. (2015) and Giesbrecht et al. (2010) studies had surprising results with the opposite findings of Rogers et al. (2008). They found an increase in blood pressure when *L*-theanine and caffeine were used concomitantly. The doses used in these two studies were much lower than in Rogers et al. (2008). Dodd et al. (2015) questioned whether there might be “differential effects of different doses and ratios” in the varying studies. The doses range from a minimum of 40 mg caffeine (Giesbrecht et al., 2010) to maximum of 250 mg (Rogers et al., 2008). The minimum dosing of *L*-theanine utilized was 36 mg (De Bruin, Rowson, Van Buren, Rycroft, & Owen, 2011) and the maximum was 250 mg (Haskell et al., 2008).

According to Haskell et al. (2013), one 200 ml cup of tea has between 25-60 mg *L*-theanine. Rogers et al. (2008) used a combination of 250 mg caffeine and 200 mg *L*-theanine, stating that is equivalent to about 6 cups of tea. The energy drink NOS® lists *L*-theanine as a component of its proprietary blend but does not specify the quantity in its

product.

L-phenylalanine. Of the six drinks, *L*-phenylalanine is found only in 5-Hour Energy® (Appendix A.1). Phenylalanine is commercially available in three forms - *L*-phenylalanine, *D*-phenylalanine, and *DL*-phenylalanine. Only the *L*-phenylalanine form is an essential amino acid and is found in proteins such as meat, fish, eggs, cheese, and milk (NMD). Any excess phenylalanine not used for protein synthesis is converted to tyrosine, tyrosine is then converted to *L*-DOPA which is a precursor to dopamine, adrenaline, and noradrenaline (Strasser, Sperner-Unterweger, Fuchs, & Gostner, v 2016; Robakis & Fahn, 2015).

Phenylalanine, both the *L* and *DL* forms, are GRAS when used in accordance with good manufacturing or animal feeding practice (FDA Phenylalanine, 2017).

There are three psychiatric medication interactions with *L*-phenylalanine that are of concern: levodopa (*L*-dopa), neuroleptics, and MAOI's. First, the use of levodopa with higher plasma phenylalanine levels can exacerbate tardive dyskinesia in some patients (Virmani, Tazan, Mazzoni, Ford, & Greene, 2016; Richardson, 2006; Mosnic, Spring, Rogers, & Baruah, 1997), as well as some of the symptoms of Parkinson's disease (Obeso et al., 2000; Nutt & Fellman, 1984). As previously described, the production of dopamine is one result of *L*-dopa's conversion of excess phenylalanine via conversion of tyrosine. The additive effects of dopamine production through both levodopa and phenylalanine contribute to these movement disorders (Robakis & Fahn, 2015).

The next interaction of concern is *L*-phenylalanine with neuroleptics and again involves tardive dyskinesia. "Abnormalities of *L*-phenylalanine metabolism may contribute

to the development and severity of tardive dyskinesia in some neuroleptic-treated unipolar depressed patients” (Gardos, Cole, & Matthews, 1992).

The third interaction is *L*-phenylalanine with non-selective MAOI’s which can result in increased risk of hypertensive crisis via accumulation of tyramine. The monoamine oxidase (MAO) enzyme occurs in two isoforms, A and B (Johnston, 1968). MAO-A is active in the gastrointestinal system where it deaminates tyramine. When MAO-A is inhibited, tyramine is not deaminated, and is therefore absorbed through the gut. Once it reaches the brain, it acts as a false neurotransmitter and displaces stored norepinephrine. This “dumping” of norepinephrine is what causes the hypertensive crisis (Robakis & Fahn, 2015). A low-tyramine diet must be maintained while on non-selective and MAO-A inhibitors. Silkaitis and Mosnaim (1976) warn against consumption of phenylalanine while taking the non-selective MAOI pargyline. As of 2007, pargyline is off the market in the US. Currently prescribed non-selective and MAO-A inhibitors include isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate).

MAO-B, on the other hand, does nothing to the tyramine in the gastrointestinal system. When used in recommended doses, MAO-B inhibitors do not carry the same dietary restrictions as the non-selective and MAO-A’s. MAO-B inhibitors include selegiline (Emsam), rasagiline (Azilect), and safinamide (Xadago).

*N*-acetyl *L*-tyrosine. *N*-acetyl *L*-tyrosine is found in only one of the six drinks (Appendix A.1). “*N*-acetyl *L*-tyrosine (NAT) is the highly soluble precursor to the conditionally essential amino acid *L*-tyrosine. For most people, it is a non-essential amino acid, but for those with phenylketonuria (PKU), it is an essential amino acid that must be

added to their diet. *L*-tyrosine is found in food sources as well as is produced from phenylalanine. *L*-tyrosine undergoes a number of chemical reactions in the process of being utilized for the production of the neurotransmitters dopamine, norepinephrine, and epinephrine. It is also a precursor to the thyroid hormone thyroxine (T4) (Parker & Brotchie, 2011; L-Tyrosine, 2007; Magnusson, Ekman, Wångdahl, & Warren, 1989).

Tyrosine (the *L*-form only) has GRAS status (FDA, 2014 December 16).

The typical daily dosage is 100-150 mg/kg. Side effects of occasional nausea, diarrhea, headaches, vomiting, and insomnia have been reported with doses over 150 mg/kg daily (L-Tyrosine, 2007).

There are two interactions between tyrosine and medications need to be considered. The first one is it can decrease the effectiveness of levodopa due to competition for absorption in the small intestine (L-Tyrosine, 2007). If both are necessary, they are to be taken at least two hours apart. Secondly, because it is a building block of thyroxine (T4), taking it with thyroid medication can potentially lead to hyperthyroidism. This is important for patients who take psychiatric medications such as lithium which can also affect thyroid hormone levels (McFarlane et al., 2011; L-Tyrosine, 2007).

Citicoline. Citicoline is an ingredient in only one of the six drinks (Appendix A.1). Once ingested, it is hydrolyzed to cytidine and choline, both of which play important roles in the production of the phospholipids involved in neuronal membrane protection, function, and repair (Weiss, 1995). It also exerts an effect on neurotransmitter levels through increasing levels of norepinephrine, dopamine, serotonin, and acetylcholine in various regions of the brain (see the review by Wignall and Brown (2012) and the

references cited therein). Recent psychiatric-focused studies have begun to look at citicoline as a potential supplement in the treatment of dual diagnoses of bipolar and substance abuse (Brown et al., 2015; Wignall & Brown, 2012; Brown & Gabrielson, 2012), as well as for depression in the elderly (Kalyn, Gavrilova, Safarova, & Shipilova, 2016) and for preserving cognitive functioning following Electro-Convulsive Therapy (ECT) (Vaithiyam, 2012).

In relation to this current research regarding energy drinks, a study that examined citicoline as a component in a beverage showed a positive impact on electroencephalogram (EEG) measures (Bruce, 2012). A subsequent study by Bruce and colleagues (2014) found improvements in sustained attention, cognitive effort, and reaction times after ingestion of a citicoline-caffeine beverage. Neither of these studies measured the singular effect of citicoline, but rather included it in beverages that also contained caffeine, as well as choline, lycopene, and Vitamin E.

Under the proprietary name, Cognizin® citicoline achieved self-affirmed GRAS status in 2009 (Kyowa, 2014).

There are no listed interactions for citicoline with prescribed psychotropic medications in the Natural Medicines Database.

Doses up to 2000 mg/day have been observed to be safe. Most common side effects were stomach pain and diarrhea (Conant & Schauss, 2004). 5-Hour Energy® does not specify the dose of citicoline in its product.

Malic acid. Malic acid is also only in one drink (Appendix A.1). It is an organic acid found in wines and fruits and used in products as a flavor enhancer, flavoring agent and adjuvant, as well as a pH control agent.

Malic acid has GRAS status. “Current good manufacturing practice results in a maximum level, as served, of 3.4 percent for nonalcoholic beverages” (FDA Malic acid, 2017). According to the NMD, “there is insufficient reliable information available about the safety of using malic acid in medicinal amounts.” The one energy drink that contains malic acid does not list the amount contained in its drink.

There are no listed interactions for malic acid with prescribed psychotropic medications in the Natural Medicines Database.

Milk Thistle extract. Milk thistle extract is in only one of the six energy drinks (Appendix A.1). Milk thistle is native to Europe and was introduced into North America by early colonists (NMD). The extract obtained from the seeds consists of seven flavonolignans, of which silybin A, silybin B, and isosilybin B are found in much higher concentrations relative to the other four (isosilybin A, silychristin A and B, and silydianin) (Kawaguchi-Suzuki et al., 2014).

Side effects reported include a mild laxative effect and gastrointestinal upset. Doses up to 840 mg per day have been used in studies evaluating the effect of milk thistle on liver function (Mayer, Myers, & Lee, 2005).

In 2001, a submission to the FDA for GRAS status was refused. “FDA has evaluated the data and information in GRAS Notice No. GRN 000066 as well as other availa-

ble information. The notice does not provide a sufficient basis for a determination that milk thistle extract is GRAS under the conditions of its intended use” (CFR, 2001).

Previous research studies investigating potential interactions between medications and milk thistle products have generated inconsistencies and contradictory results between *in vitro* and *in vivo* study results. For the interested researcher, both NMD and Hermann & Von Richter (2012) provide thorough discussions regarding these competing studies.

A more recent attempt to understand milk thistle's effect on the cytochrome P450 enzyme was conducted by Kawaguchi-Suzuki et al. (2014). Their results “suggest little potential for significant drug interactions when milk thistle extracts are used concurrently with the majority of currently marketed drugs metabolized by CYP1A2, CYP2C9, CYP2D6, and CYP3A4/5.” However, a few important caveats to their study should be noted. First, poor metabolizers of CYP2D6 were not included in the study. Some psychiatric drugs metabolized by CYP2D6 include imipramine (Tofranil), amitriptyline (Elavil); haloperidol (Haldol), risperidone (Risperdal), chlorpromazine (Thorazine); and propranolol (Inderal) (NMD).

Second, CYP2C9 genotyping was not considered. Some psychiatric drugs metabolized by CYP2C9 include amitriptyline (Elavil) and diazepam (Valium) (NMD).

Also, the activity of multiple other P450 enzymes (i.e., CYP2A6, CYP2B6, CYP2C8, and CYP2C19) was not measured. A significant number of psychiatric medications impacted by these enzymes include valproic acid (Depakote), disulfiram (Antabuse), bupropion (Wellbutrin), selegiline (Emsam), methadone, carbamazepine

(Tegretol), citalopram (Celexa), escitalopram (Lexapro), and sertraline (Zoloft) (Flockhart, 2007).

The effect of milk thistle on the clearance of drugs that undergo glucuronidation was also not studied. Some drugs that are metabolized by glucuronide conjugation include oxazepam (Serax), haloperidol (Haldol), and lamotrigine (Lamictal) (NMD).

Sweeteners. Sweeteners used include sugar, glucose, sucrose, sucralose, high fructose corn syrup, and maltodextrin. A comprehensive review of these sweeteners is beyond the scope of this current thesis, other than to point out the already increased risk of potentially developing Metabolic Syndrome and/or Type 2 diabetes for patients who take psychotropic medications, particularly atypical antipsychotics.

### Literature

The second section of this literature review will focus on the current information regarding energy drink consumer's knowledge. There exists a significant lack of research related to consumer's knowledge regarding their energy drink ingredient's potential interactions with their prescribed psychotropic medications. A PubMed literature search using keyword combination “energy drink,” with a 20-year date range (01/01/96-01/01/16), (the first energy drink being introduced to the US in 1997), and the filter “humans,” produced 2587 articles.

The research focus of this study is on knowledge, or per the PAPM stage 1 – “unaware of the issue,” thereby potentially placing oneself at risk. With the PAPM stage 1 framework as the guiding principle, the above articles were narrowed down to only

those that included some form of direct question to, or measurement of, consumer's knowledge of energy drink ingredients. Of the resulting articles, none were found that specifically referenced consumer knowledge of potential interactions between energy drink ingredients and psychiatric medications.

Of the few studies that did include directed questions regarding ingredients, there was no continuity in the types of questions asked. Some studies focused on caffeine by measuring awareness of caffeine content but did not ask about other ingredients (Usman, Bhombal, Jawaid, & Zaki, 2015; Kim, Y.J. et al., 2015; Ward, 2009). One study asked directly, "Do you know that the principal ingredient of energy drinks is caffeine (or taurine)?" (Kim, Y.J. et al., 2015). A few studies asked respondents to pick ingredients and/or energy drinks out of multiple choice lists (Babwah et al., 2014; Aslam et al., 2013; Faris, 2014; Attila & Çakir, 2011). Confusing energy drinks with sports drinks or soft drinks were also reported (Hidriroglu, Tanriover, Unaldi, Sulun, & Karavus, 2013; Musaiger & Zagzoog, 2013; Attila & Çakir, 2011; Costa, Hayley, & Miller, 2014; Aslam et al., 2013).

While investigating college student's energy drink consumption, Faris (2014) directly asked if they had read the ingredient list of the energy drink to which almost two-thirds reported they had not. Attila and Çakir, (2011) found little more than half "reported that they 'knew' the ingredients of energy drinks." Almost 26% of respondents in the study by Kim and Kim (2015) reported they were "well acquainted" with the ingredients of their drinks. Participants in Peymani et al. (2012) were able to name at least two ingredients, but the study did not provide a compiled list of those responses.

Those studies also did not have a consistent population group. Some focused on

children and adolescents (Costa et al., 2014; Babwah et al., 2014; Musaiger & Zagzoog, 2014), college students (Ward, 2009; Kim et al., 2015; Faris, 2014; Attila & Çakir, 2011), medical/nursing students (Aslam et al., 2013; Usman et al., 2015; Hidiroglu et al, 2013, Kim & Kim, 2015; Ghreiz et al., 2015) and adult bodybuilders (Peymani et al., 2012).

The population groups were also spread across the world. Studies originated in the United States (Faris, 2014, and Ward, 2009), Australia (Costa et al., 2014), Korea (Kim & Kim, 2015; Kim et al., 2015), Pakistan (Usman et al., 2015; Hidiroglu et al., 2013; Aslam et al., 2013), Turkey (Attila & Çakir, 2011), Saudi Arabia (Musaiger & Zagzoog, 2013; Ghreiz et al., 2015), Trinidad and Tobago (Babwah et al., 2014), and Iran (Peymani et al., 2012).

Anticipating by virtue of their academics, medical and nursing students would be most knowledgeable about medications and interactions compared to other college students and younger consumers, surprisingly only 25.9% of Korean nursing students self-reported they were “well acquainted with the ingredients of the drinks they consumed.” Per the study results, 28.9% of the nursing students knew caffeine was in energy drinks, but fewer knew about taurine (19.3%), glucose (14.9%), citric acid (9.1%), vitamin C (7.4%) minerals (5.9%), carbonic acid (5.0%), vitamin B (2.8%), herbal medicines (2.5%), nicotine (1.8%), alcohol (0.8%), protein (0.6%), and other contents (0.1%) (Kim & Kim, 2015). In Saudi Arabia, a majority of medical students did not know caffeine was the main ingredient, nor that other stimulants or vitamins were also ingredients (Ghreiz et al., 2015).

Medical students in Pakistan and Turkey were confused about the differences between energy drinks and sports drinks, indicating a serious lack of knowledge

regarding energy drink ingredients (Hidiroglu et al., 2013; Aslam et al., 2013).

## METHODS

Participants and procedures

Semi-structured interviews were conducted with six psychiatric patients in a northwestern state of the USA. Recruitment of participants consisted of providing local psychiatric providers a description of the study, with the request they assist with the selection from their patients using the following inclusion criteria:

- over the age of 18 years old,
- noted to have been drinking energy drinks, either through direct observation or through disclosure to their provider,
- whom the provider considers psychiatrically stable enough to participate in an interview
- have requested their psychiatric medication refills in a consistent and timely manner over the previous six months,
- history of reliability in keeping appointments for adequate post-interview follow-up,
- agreeable to the interview being audio recorded,
- agreeable to providing a medication list.

Excluded are those:

- under the age of 18 years old,
- not known to be an energy drink consumer,
- actively psychotic, or at significant risk of psychiatric destabilization, per the provider's judgment,
- unreliable or inconsistent with medication refills and/or keeping appointments,
- unwilling to allow for audio recording,
- unwilling to provide medication list.

When the provider received initial verbal agreement from their patient, they provided this researcher with the participant's preferred contact method. This researcher contacted the participant to arrange the interview date and time. The researcher requested the participant bring 1: their medication list, and 2: a list of brand(s) of energy drink they

consume, with them to the interview. The interview setting was a private office space within the referring provider's larger office. Interviews were conducted during normal business hours. Informed consents (Appendix B.1 and B.2) were obtained from all participants. This study was approved by both the Institutional Review Board of Montana State University and the Institutional Review Board of Billings.

Basic socio-demographic information was collected which included age, gender, level of education, and employment. The interviews were conducted in private, audio recorded, then transcribed verbatim by this researcher. Confidentiality was maintained through the use of an assigned number for each participant. The transcripts contained only the assigned number as the participant identifier. The assigned numbers were known only to this researcher. For the duration of the study, the audio recordings and signed consent forms were kept in a locked file cabinet for which only this researcher had access to the key. Upon graduation, the audio recordings and signed consent forms will be handed over to the College of Nursing Campus Director in Bozeman, MT for disposal per Montana State University policy.

### Measures

Five open-ended questions were developed for this study (Figure #2). The questions were adapted from interview questions utilized in a 2014 Thai study which sought to uncover reasons for pre-dialysis patients use, and non-use, of herbal and dietary supplements (Tangkiatkumjai, Boardman, Praditpornsilpa, & Walker, 2014.) In line with PAPM's Stage 1 – “unaware of the issue,” these questions target patient's underlying

reasons for initial usage, as well as their thoughts on safety in regards to their dialysis treatment and kidney medications.

In the strength of the semi-structured interview method, each question allowed for further probe questions in order to elicit specific information if not provided spontaneously (Barriball & While, 1994). The questions were piloted with self-selected volunteers from this researcher's social circle.

Figure 2 - 5 Item Interview Questions (With Probes)

1. Tell me about how and when you started drinking Energy Drinks (ED).
  - What is your ED of choice? How many do you drink in a day/week/month?
  - What led you to start drinking ED?
  - What did you hope drinking ED would achieve?
  - Who/what influenced you to start drinking ED?
  
2. Tell me what you know about the ingredients of your ED.
  - What is your understanding of what makes an ED different from any other drink?
  - Have you ever read the ingredient list on the can?
  - Tell me which of the ingredients you remember at the moment.
  
3. Which did you start first - the ED or psychiatric medication?
  - Ages?
  
4. Have you discussed the use of your ED with your psych med prescriber?
  - What do you remember about that discussion?
  
5. Are you aware of any interactions between your psych meds and the ingredients of your ED?
  - If yes, what interactions?
  - Where did you get your information?
  - Once you had the information, did you make any changes, either to the ED, or the medication?

Analysis

Descriptive, content and comparative analysis were utilized as ways of looking at the data gathered.

## RESULTS

This study examined energy drink consumer's knowledge of potential ingredient interactions with their mental health medications. The six participants ranged in age from 22-62 years old ( $n = 6$ ; median age = 33; mean age = 36.5) (Table 8). Five were men, and one was a woman. 50% were high school educated, 33% had "some college," and 17% were college graduates. 67% used over-the-counter supplements (multivitamin, Vitamin B12, Vitamin D, calcium, and melatonin). Three of the six were already consuming energy drinks prior to starting psychotropic medication. Two-thirds endorsed having spoken with their provider about their energy drink use.

Table 8 Sample characteristics ( $n = 6$ )

	n	%
Age		
18 - 24	2	33
25 - 49	4	67
50+	1	17
Gender		
Men	5	83
Women	1	17
Education level		
High school	3	50
Some college	2	33
College graduate	1	17
Supplement use		
Yes	4	67
No	2	11
First use		
Energy drink	3	50
Medication	3	50
Spoke with provider		
Yes	4	67
No	2	11

In response to interview Question # 1 which targeted the underlying themes for beginning the consumption of energy drinks, the most often reported theme by all participants was for energy and motivation (Figure 3). This was followed closely by assistance in staying awake/alert, taste/flavor, and “other” (i.e., kids at home, always around, another new product, advertisements on television, treat for oneself, influence of friends, cost, etc.) The least cited reason was “work.”

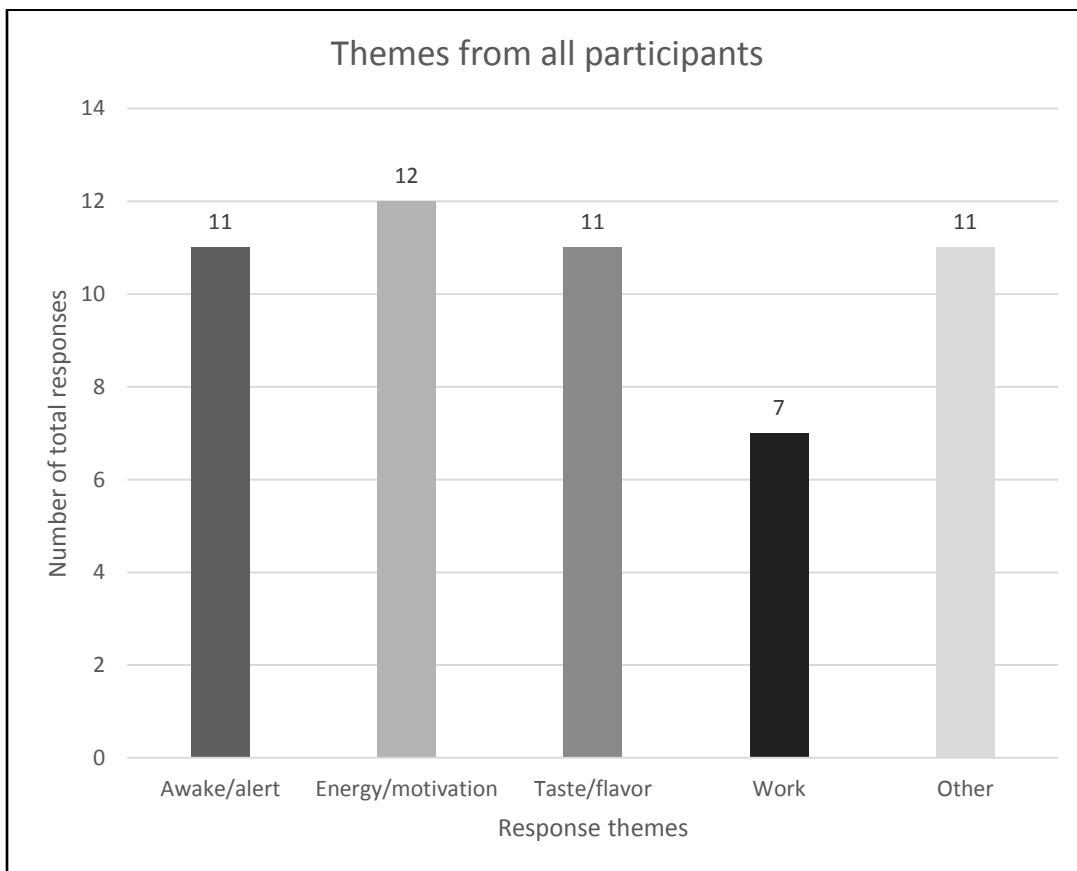


Figure 3. Themes from all participants in response to Question #1 – Tell me about how and when you started drinking energy drinks.

Figure 4 illustrates the responses in each theme category by the individual participant.

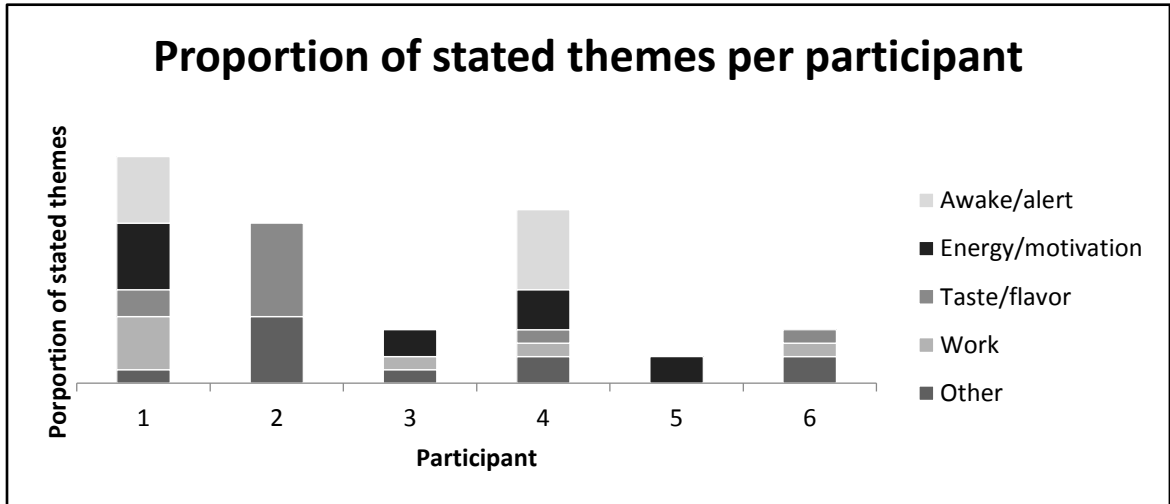


Figure 4. Proportion of stated themes per participant

Question # 2 targeted participants knowledge of the energy drink ingredients (Figure 5). All six participants were able to name at least two ingredients. Three participants named three ingredients. Five ingredients were named by one participant.

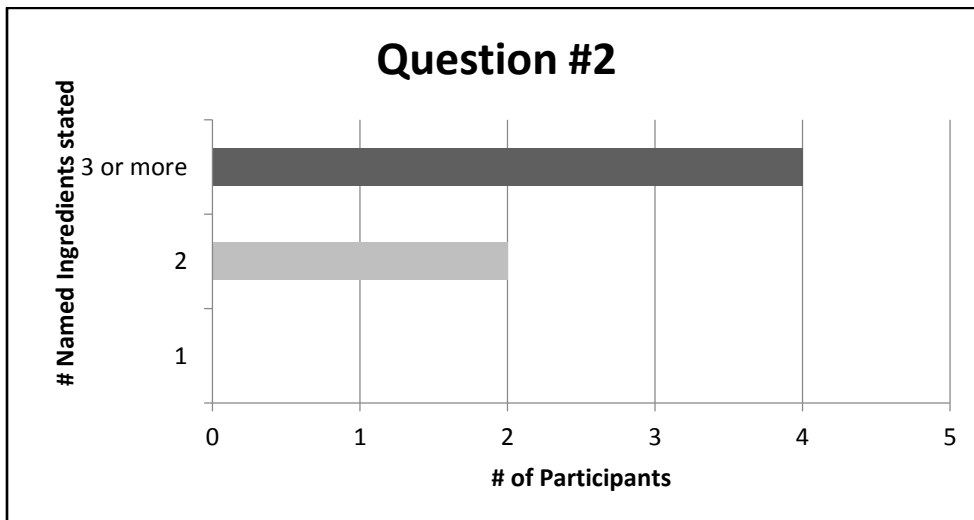


Figure 5. Question #2 – Tell me what you know about the ingredients of your energy drink.

The responses to Question # 3 were equally divided between those who were drinking energy drinks prior to starting psychotropic medication and those who started medications prior to energy drink consumption (Figure 6).

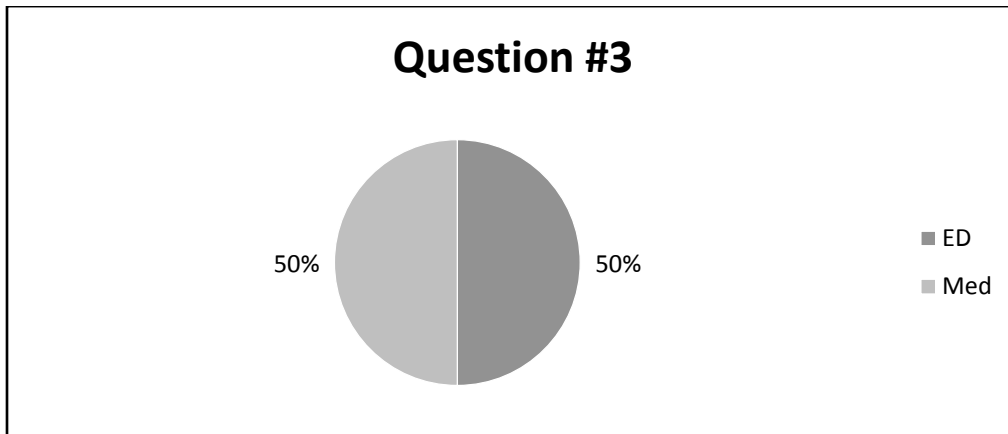


Figure 6. Question # 3 – Which did you start first, the energy drink or psychiatric medication?

The fourth question involved participants informing their psychotropic medication prescriber about their energy drink use (Figure 7). Two-thirds reported having discussed their energy drink use with their prescriber.

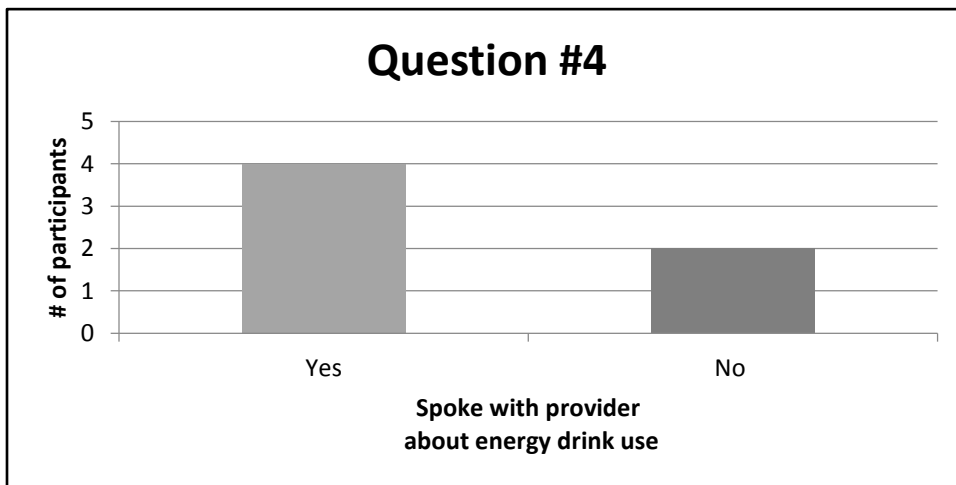


Figure 7. Question #4 – Have you discussed the use of your energy drink with your psych med prescriber.

Where the first four interview questions focused on background information, the answers provided to the fifth question were specific to the purpose of this study. Even though all six participants made judgment statements during the interviews about the energy drinks being “bad”, when asked specifically if they were aware of any interactions between their psychotropic medications and the ingredients of their energy drinks, only 33% were able to state at least one ingredient/medication interaction (Figure 8).

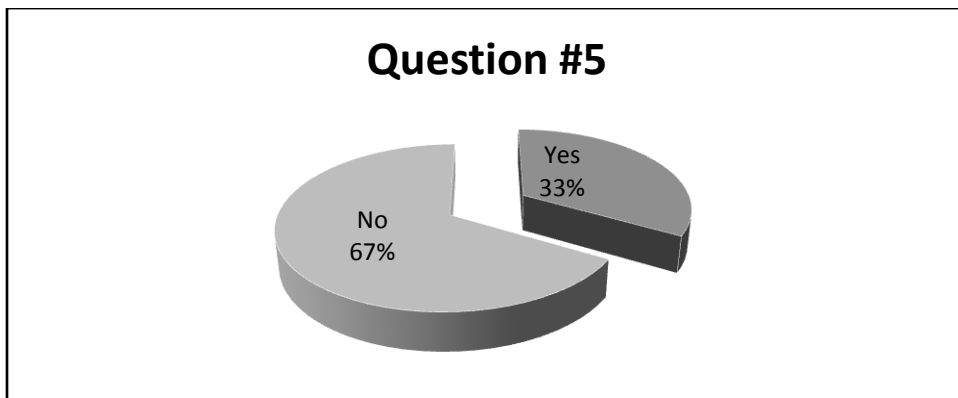


Figure 8. Question #5 – Are you aware of any interactions between your psych meds and the ingredients of your energy drinks?

### Summary of Results

The main finding of this qualitative study was that two-thirds of the participants did not know if there were any interactions between the ingredients of their energy drink with their psychotropic medications.

All participants named at least two ingredients but the oldest and youngest participants were the only two who verbalized an ingredient/medication interaction. These two participants shared some other similarities. Both said they had had conversations with their providers regarding their energy drinks and their medications. Although there were more interactions of concern, both cited only caffeine as being problematic, the youngest

with his lithium (“It kind of acts like an accelerant. It’s like pouring gasoline or kerosene onto a fire and watching it go into a blaze”) and the oldest with his Concerta® (methylphenidate) (“...ramping up your blood pressure and heart rate and stuff”).

Neither spoke of any other ingredients or interactions. With no previous targeted research available to use as a guide, an assumption was made prior to beginning the interviews that there would be a lack of knowledge about potential interactions. Thus, built into the study as a safety precaution, *Natural Medicines* database was used to check for any ingredient/medication interactions. Post-interview, the results were printed and given to their prescriber for discussion at their professional discretion. No life-threatening interactions were found although there were some of concern (Appendices A.3-A.8).

Regarding health behavior, having spoken with one’s provider about their energy drink consumption appeared to be a positive force for change. Of the four participants who stated they had spoken with their provider, two decreased (but did not discontinue) the amount of energy drink use as a result of that discussion, one changed the timing of his medications, and one made no change. To what extent the strength of the provider-patient working alliance impacted those individual decisions is not known.

An interesting and unexpected finding arose out of these interviews. Despite no questions in this regard, all of the participants made unsolicited comments about energy drinks being “bad” (“I’m sure they’re bad”, “It’s probably not in my best interest to drink those”, “...they’re not very good for you”, “...this stuff’s bad for you”, “...told me it wasn’t too good for me”, “I know there’s some bad (ingredients)... other than not that great for you.”)

However, their perception of them being “bad” did not deter their choice to consume their chosen energy drinks. Any perceived detriment was overridden by their justifications for use, citing themes of “energy/motivation” (23%), followed closely by “awake/alert”, “taste/ flavor”, and “other” (i.e., kids at home, always around, another new product, advertisements on television, treat for oneself, influence of friends, cost, etc.), all at 21%. “Work” was the least cited theme at 13%. None made reference to energy drink use as being related to problems or side effects of their psychiatric medications.

## DISCUSSION

The assumption of this research was that study participants would be in the PAPM's Stage 1 – “unaware of the issue.” With two-thirds of the participants stating they were not aware of any interactions between their energy drink ingredients and their psychotropic medications, the assumption was partially true. However, by virtue of being recruited, and the study premise being explained for informed consent, staying in Stage 1 and remaining unaware became impossible. As a result of being asked to be interviewed they shifted into one of the other stages: Stage 2 - “unengaged by the issue,” Stage 3 - “undecided about acting,” Stage 4 - “decided not to act,” or Stage 5 - “decided to act.” Stages 6 and 7 (“acting” and “maintenance”) would apply to the participants who had already adopted the precaution and made changes in either their energy drink consumption or medication timing.

While a multitude of possibilities exists as to where the perception of “bad” came from (i.e., media reports of deaths, discussion with medical providers, friends, family, etc.), the question “Why continue if you think it’s bad?” came to the surface for this researcher after the interviews ended. Although there are a variety of health behavior and decision-making models one could reference, the theoretical framework of this study is based on the Precaution Adoption Process Model (PAPM). The PAPM, in combination with Wilde’s (1998) Risk Homeostasis Theory (RHT), provides some understanding of consumer’s decision making about risk-taking.

PAPM’s goal is “to explain how a person comes to the decision to take action, and how he or she translates that decision into action” (Weinstein et al., 2008). Once engaged

by the issue (i.e., the risk of continuing energy drink consumption), one is either undecided about acting (Stage 3) or has decided to act (Stage 5), or not act (Stage 4), upon the information. RHT fits into this area within the Stages of decision-making. Wilde (1998, 2014) explains the “four utility factors” in the decision-making process regarding risk: 1) the expected benefits of risky behavior alternatives; 2) the expected costs of risky behavior alternatives, 3) the expected benefits of safe behavior alternatives, and 4) the expected costs of safe behavior alternatives.

Wilde (1998) writes, “The level of risk at which the net benefit is expected to maximize is called the target level of risk in recognition of the realization that people do not try to minimize risk (which would be zero at zero mobility), but instead attempt to optimize it. Risk homeostasis theory posits that people at any moment of time compare the amount of risk they perceive with their target level of risk and will adjust their behavior in an attempt to eliminate any discrepancies between the two.” A possible explanation for the participants in PAPM Stages 1-4 is they had lower levels of perceived risk and higher target levels of risk. Discussion with their provider and educational materials may be starting points to lessen/optimize the gap between perceived and target, thereby encouraging change. Those participants in Stages 6 and 7 are assumed to have higher levels of perceived risk and lower target levels of risk. Gaining understanding as to the internal processes that sustain them in these higher stages is fruit for another study.

#### Limitations of the Study

“Statistical analysis with small samples is like making astronomical observations with binoculars” (“Best Practices,” n.d.). With an *n* of only 6, this study barely peeks into

the vast expanse that is the intersection of mental health, patient health knowledge, energy drinks, and psychotropic medications.

Along with a small  $n$ , other limitations are also present in this study. First, all participants were recruited from three local mental health clinics in a western US city that is 85.6% Caucasian (Billings, MT, n.d.). Homogeneity was clearly evident in that all six participants were Caucasian. The same questions asked in different parts of the country, and with more racial diversity of the participants, may reveal different results.

Second, while the current interview questions were structured after a 2014 Thai study which sought to uncover reasons for pre-dialysis patients use, and non-use, of herbal and dietary supplements (Tangkiatkumjai et al., 2014), they were not tested on their own merits for validity and reliability. Therefore, descriptive, content, and comparative analysis were the approaches used to engage the data.

Third, this researcher is a registered nurse at one of the clinics the participants were recruited from and works directly with them regarding their mental health care. While this familiarity may have provided a layer of trust, it could also unconsciously have biased the responses into answers the participants thought this researcher wanted to hear, rather than the reality in their day-to-day lives.

### Recommendations for further research

A recent article by Smoyak, Swarbrick, Nowik, Ancheta, and Lombardo (2017) points out, “Although there have been studies of different populations, varying by age and socioeconomic status, none have had, as participants, individuals with mental illness.” Despite this current researcher’s work being a qualitative study with a small sam-

ple, this study is the first (to this researcher's knowledge) to directly explore energy drink consumer's knowledge of interactions between the ingredients of their drink and their psychotropic medications. Exploring this with a much larger, and more diverse, sample would contribute to potential generalizability. If the results bear out that a significant number of participants are unaware of any interactions thus potentially putting themselves at risk for adverse events, a targeted education initiative could be developed.

In the same article, Smoyak et al. (2017) also wrote, "Nothing is currently known about whether individuals with mental illness use HED (high energy drink) to offset their symptoms, or whether their use began after diagnosis or after psychoactive drugs were prescribed and taken as ordered." This researcher would like to share her findings on two of these three points. First, although not asked directly, none of the participants in this current work made reference to energy drink use as being related to problems or side effects of their psychiatric medications. Secondly, while diagnosis information was not collected, the researcher did specifically ask the question, "Which did you start first, the energy drink or the psychiatric medication?" to which responses were evenly divided. A more in-depth understanding of the reasons behind energy drink consumption among those who take psychotropic medications will help providers as they consider the impact the medications may be having on their patients.

## CONCLUSION

As the use of energy drinks continues to increase, there is much to be learned about their use (Richards & Smith, 2016) and potential ingredient interactions in conjunction with psychotropic medications. The variety of ingredient formulations in all the drinks available on the market is infinite, making the review of each individual product extremely time-consuming and beyond the scope of this study. The literature review in this study provides an overview of the ingredients of the five top-selling energy drinks and the top-selling energy shot. Some ingredients of the drinks used by consumers in this study were not covered in the literature review. These included green tea extractives, yerba mate leaf extract, beta-alanine, *L*-Leucine, *B*-phenylethylamine hcl, *L*-Valine, *L*-Isoleucine, yohimbine, *N*-Methyl tyramine, evodia, toothed clubmoss, 5-HTP, and vinpocetine. This underscores the necessity of the clinician exploring their patient's ingredients in relation to their prescribed medications.

In their 2014 article "Caffeine-containing energy drinks: beginning to address the gaps in what we know" Sorkin and Coates summarized existing concerns regarding energy drink consumption. "Many critical gaps in our understanding of CCED's (caffeine-containing energy drinks) remain to be addressed. Among these are the contribution of ingredients other than caffeine and sugar to the metabolic, physiologic, and behavioral effects of CCEDs, elucidation of the mechanisms of underlying the modulation of alcohol response by CCEDs, and better data on the prevalence of use of CCEDs and on their acute and long-term effects on appetite, metabolism, BMI, alertness, sleep patterns, and cognition." This researcher would add "psychotropic medications."

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APPENDICES

APPENDIX A

STUDY PARTICIPANT'S ENERGY DRINKS

Appendix A.1: 5 Top Selling Energy Drinks/ Shots in 2015

	Caffeine	Guarana	Ginseng, panax	Taurine	Other	Sweetener	B6 (pyridoxine hcl)	B12 (cyanocobalamin)	B3 (niacin)	B5 (pant. Acid)	B2 (riboflav)	B9 (Folic acid)	Caffeine Content mg/bevera	mg/1 oz
NOS	✓	✓		✓	L-theanine	HFCS and sucralose	✓	✓					160 mg/16 fl oz	10
CMLX6: caffeine, guarana, B12, B6, L-theanine, taurine														
Red Bull	✓			✓		sucrose and glucose	✓	✓	✓	✓			80 mg/8.4 fl oz	9.5
Amp	✓	✓	✓	✓		HFCS	✓	✓	✓	✓	✓		142 mg/16 fl oz	8.9
Monster	✓	✓	✓	✓	L-carnitine, D-glucuronolactone, L-tartarate, inositol, salt	sugar, glucose, sucrose, and maltodextrin	✓	✓	✓		✓		160 mg/16 fl oz	10
Energy blend: glucose, taurine, panax ginseng extract, L-carnitine, caffeine, glucuronolactone, inositol, guarana extract, maltodextrin														
Rockstar	✓	✓	✓	✓	L-carnitine, glucuronolactone, inositol, milk thistle extract	sugar, glucose	✓	✓	✓	✓	✓		160 mg/16 fl oz	10
In Each Serving: taurine, guarana seed extract, caffeine, glucuronolactone, L-carnitine, inositol														
5-Hour Energy	✓			✓	glucuronolactone, N-Acetyl L-Tyrosine, L-Phenylalanine, citicoline, malic acid, folic acid	sucralose	✓	✓	✓	✓	✓	✓	200 mg/1.93 fl oz	103.6
Energy Blend: taurine, glucuronic acid (as or from glucuronolactone, malic acid, N-Acetyl L-tyrosine, L-phenylalanine, caffeine, citicoline														

Appendix A.2a: Study Participant’s Energy Drinks

	Caffeine	Guarana	Ginseng, panax	Taurine	Other	Sweetener	B6 (pyroxi dine hcl)	B12 (cyano cobal in)	B3 (niaci n)	B5 (pant. Acid)	B2 (riboflav)	Caffeine Content mg/beverage	mg/1 oz
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Rockstar													
Revolt													
-Killer grape	✓	✓	✓	✓	milk thistle extract, malic acid, glucuronolactone, inositol	sugar, acesulfame potassium, sucralose	✓	✓	✓	✓		240 mg/16 oz	15
In each serving: taurine 1000 mg, caffeine 120 mg, glucuronolactone 50 mg, inositol 25 mg													

-Whipped Strawberry	✓	✓	✓	✓	milk thistle extract, glucuronolactone, inositol, skim milk, cream	sugar, glucose	✓	✓	✓	✓		160mg/16 oz	10
In each serving: taurine 1000 mg, caffeine 80 mg, glucuronolactone 50 mg, inositol 25 mg													

Rockstar													
-Zero Carb	✓			✓	green tea extractives, yerba mate leaf extract, malic acid, L carnitine	sucralose, acesulfame potassium	✓	✓	✓	✓		240mg/16 oz	15
Energy Blend 1.27g (taurine 1000 mg, caffeine 120 mg, green tea extract 100 mg, L-carnitine 25 mg, yerba mate leaf extract 25 mg)													

Xyience													
-all flavors	✓	✓	✓	✓	glucuronolactone, L carnitine, inositol	sucralose, acesulfame potassium	✓	✓	✓	✓		176 mg/16 oz	11.6

Kickstart													
-Hydrating Boost	✓					HFCS, acesulfame potassium, sucralose						68mg/12 oz	5.7
-Recharge	✓					HFCS, acesulfame potassium, sucralose						68mg/12 oz	5.7
-Energizing	✓					HFCS, acesulfame potassium, sucralose						90-92mg/16oz	5.6-5.7

Appendix A.2b: Study Participant’s Energy Drinks

	Caffeine	Guarana	Ginseng, panax	Taurine	Other	Sweetener	B6 (pyroxi dine hcl)	B12 (cyanoc obalam in)	B3 (niaci n)	B5 (pant. Acid)	B2 (riboflav)	B9 (Folic acid)	Caffeine Content mg/beverage	mg/1 oz
<b>Monster Energy</b>														
-Ultra Sunrise	✓	✓	✓	✓	L-carnitine, L-tartrate, salt, glucuronolactone, inositol	erythritol, sucralose, acesulfame potassium	✓	✓	✓	✓			150mg/16 oz	9.3
Energy Blend: taurine, panax ginseng extract, L-carnitine, caffeine, guarana extract, glucuronolactone, inositol														
-Ultra Citron	✓	✓	✓	✓	L-carnitine, L-tartrate, salt, glucuronolactone, inositol	erythritol, sucralose, acesulfame potassium	✓	✓	✓	✓			152mg/16 oz	9.5
Energy Blend: taurine, panax ginseng extract, L-carnitine, caffeine, guarana extract, glucuronolactone, inositol														
<b>Redline Xtreme</b>														
Proprietary Blend: Beta-Alanine, Caffeine Anhydrous, L-Leucine, B-Phenylethylamine HCL, L-Valine, L-Isoleucine, N-Acetyl-L-Tyrosine, Yohimbe, N-methyl Tyramine, Evodia, Toothed Clubmoss, 5-HTP, Yerba Mate Extract, Green Tea Extract, Virpocetine														
Amp	✓	✓	✓	✓		HFCS	✓	✓	✓	✓	✓	✓	142 mg/16 fl oz	8.9
Red Bull	✓			✓		sucrose and glucose	✓	✓	✓	✓			80 mg/8.4 fl oz	9.5
Green Dragon	✓			✓		acesulfame potassium, sucralose	✓	✓	✓	✓			47 mg/8.4 oz	5.6
Energy Blend (104 mg): Inositol, 50 mg; caffeine 47 mg; taurine 7 mg														
Rockstar	✓	✓	✓	✓	L-carnitine, glucuronolactone, inositol, milk thistle	sugar, glucose	✓	✓	✓	✓	✓	✓	160 mg/ 16 fl oz	10
In Each Serving: taurine, guarana seed extract, caffeine, glucuronolactone, L-carnitine, inositol														

Appendix A.3 Participant #1 Interactions of Concern

Participant #1

		Ingredients																		
Energy Drink Brand	Energy Drink Variety	Caffeine	Guarana	Ginseng, panax	Taurine	Milk thistle extract	green tea extractives	yerba mate leaf extract	B6 (pyridoxine hcl)	B12 (cyanoco balamin)	B3 (inachi)	B5 (pant acid)	B2 (riboflavin)	B9 (folic acid)	Inositol	L-carnitine	L-tartrate	glucuronolactone	malic acid	
Red Bull		✓			✓				✓	✓	✓	✓								
Amp		✓	✓	✓	✓				✓	✓	✓	✓	✓							
Interaction Concerns																				
<b>Medts</b>																				
	Vyvanse®	M	M	M																
	modafinil		M	M																
	levodhroxyline																			
	naproxen		M	M																
	acetaminophen																			

Interaction Concern - MM = Major, M = Moderate, m = minor (adapted from Natural Medicines Database "Stop-Light Rating System")

Appendix A.4 Participant #2 Interactions of Concern

		Participant #2																				
		Energy Drink Brand	Energy Drink Variety	Caffeine	Guarana	Ginseng, panax	Taurine	Milk thistle extract	green tea extractives	yerba mate leaf extract	B6 (pyridoxine hcl)	B12 (cyanocobalamin)	B3 (niacin)	B5 (pantoic acid)	B2 (riboflavin)	B9 (folic acid)	Inositol	L-carnitine	L-tartaric acid	glucuronolactone	malic acid	
Red Bull				✓			✓				✓	✓	✓	✓								
Green Dragon			✓				✓				✓	✓	✓	✓								✓
<b>Meds</b>		<b>Interaction Concerns</b>																				
	kanpraline																					
	lithium																					
	methylphenidate (Concerta®)	M																				
	ibuprofen	M																				
	omeprazole	m																				
	Flonase®																					

Interaction Concern - MM = Major, M = Moderate, m = minor (adapted from Natural Medicines Database "Stop-Light Rating System")

Appendix A.5 Participant #3 Interactions of Concern

**Participant #3**

Energy Drink Brand	Energy Drink Variety	Ingredients																	
		Caffeine	Guarana	Ginseng- panax	Taurine	Milk thistle extract	green tea extractives	yerba mate leaf extract	B6 (pyroxaline hc)	B12 (cyanoco balamin)	B3 (niacin)	B5 (panth. acid)	B2 (riboflavin)	B9 (folic acid)	Inositol	L-carnitine	L-tartrate	gliceronol acetone	malic acid
Rocksstar		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓				✓
Red Bull		✓			✓			✓	✓	✓	✓	✓							

Meds	Interaction Concerns																			
aniprazole (Abilify®)																				
fluoxetine																				
bupropion																				
Adderall XR®	M	MM	M																	
Adderall® IR	M	MM	M																	
clonazepam			M																	
calcium citrate																				
Vitamin D																				
Vitamin B12																				
multivitamin																				
omeprazole	m		M																	
Implanor®	m	m	M																	

Interaction Concern - MM = Major, M = Moderate, m = minor (adapted from Natural Medicines Database "Stop- Light Rating System")

Appendix A.6 Participant #4 Interactions of Concern

**Participant #4**

Energy Drink Brand	Energy Drink Variety	Ingredients																	
		Caffeine	Guarana	Ginseng, panax	Taurine	Milk thistle extract	green tea extractives	yerba mate leaf extract	B6 (pyridoxine hcl)	B12 (cyanocobalamin)	B3 (niacin)	B5 (pant. acid)	B2 (riboflavin)	B9 (folic acid)	Inositol	L-carnitine	L-tartate	glucuronolactone	malic acid
Monster Energy	Ultra Sunrise	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
	Ultra Citron	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
	Zero Carb	✓					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓
Rockstar																			

Meats	Interaction Concerns																			
chlorpromazine	m																			
paliperidone (Invega®)				M																
lithium ER																				
metformin																				
omeprazole	m			M																
docusate sodium																				
albuterol inh	M			M																
isotretinoin																				M

Interaction Concern - MM = Major; M = Moderate; m = minor (adapted from Natural Medicines Database "Stop-Light Rating System")

Appendix A.7a Participant #5 Interactions of Concern

Participant #5

Energy Drink Brand	Energy Drink Variety	Ingredients																		
		Caffeine	Guarana	Ginseng panax	Taurine	Milk thistle extract	green tea extractives	yerba mate leaf extract	B6 (pyroxaline kcal)	B12 (cyanocobalamin)	B3 (niacin acid)	B5 (pant. acid)	B2 (riboflavin)	B9 (folic acid)	Inositol	L-carnitine	L-tartate	glicucuronola cone	malic acid	
Red Bull	sugar free	✓			✓				✓	✓	✓	✓								
Monster		✓	✓	✓	✓				✓	✓	✓	✓	✓		✓	✓			✓	

Meds	Interaction Concerns
divalproex sodium	
risperidone	M
novolog	m m M
lanus	m m M
metformin xr-saxagipin	m m M

Interaction Concern - MM = Major; M = Moderate; m = minor (adapted from Natural Medicines Database "Stop-Light Rating System")

Appendix A.7b Participant #5 Interactions of Concern

**Participant #5**

		Ingredients												
Energy Drink Brand	Energy Drink Variety	Beta Alanine	Caffeine Anhydrous	L-Leucine	B-Phenylalanine HCL	L-Valine	L-isoleucine	N-Acetyl-L-tyrosine	Yohimbe	N-methyl Tyramine	Evodia	Toothed Clubmoss (aka Bitter Orange)	5-HTP	Vinpocetine
RedLine	Xtreme	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Meds	Interaction Concerns													
divalproex sodium														M
risperidone									M					M,m
novolog	M	m	M	M	M	M								M
lantus	M	m	M	M	M	M								M
metformin xr-saxagliptin	M	m	M	M	M	M		m						M

Interaction Concern - MM = Major, M = Moderate, m = minor (adapted from Natural Medicines Database "Stop-Light Rating System")

Appendix A.8 Participant #6 Interactions of Concern

Participant #6

Energy Drink Brand	Energy Drink Variety	Ingredients																	
		Caffeine	Guarana	Ginseng-panax	Taurine	Milk thistle extract	green tea extractives	yerba mate leaf extract	B6 (pyroxaline hcl)	B12 (cyanocobalamin)	B3 (niacin)	B5 (panthoic acid)	B2 (riboflavin)	B9 (folic acid)	Inositol	L-carnitine	Aspartate	glucuronolactone	malic acid
Rockstar Revolt	KillerGrape	✓	✓	✓	✓	✓		✓	✓	✓	✓				✓			✓	✓
	Whipped Strawberry	✓	✓	✓	✓				✓	✓	✓	✓			✓			✓	✓
Monster		✓	✓	✓	✓			✓	✓	✓	✓				✓			✓	
Amp		✓	✓	✓	✓			✓	✓	✓	✓								
Kickstart	HydratingBoost	✓																	
	Recharge	✓																	
	Energizing	✓																	
Xyience	all flavors	✓	✓	✓	✓			✓	✓	✓	✓			✓				✓	

Meds	Interaction Concerns
bupropion xl	
sertraline	M
bupropion	M
Vitamin D	
methylxanthin	

Interaction Concern - MM = Major, M = Moderate, m = minor (adapted from Natural Medicines Database "Stop-Light Rating System")

APPENDIX B

CONSENTS

Appendix B.1: Consent Form, Montana State University Institutional Review Board

**SUBJECT CONSENT FORM FOR PARTICIPATION IN HUMAN RESEARCH**  
**AT**  
**MONTANA STATE UNIVERSITY.**

**APPROVED**

**JAN 13 2017**

**IRB OF BILLING**

**Title:** Consumer's Knowledge of Energy Drink Ingredient Interaction with their Prescribed Psychotropic Medications

**Introduction:** You are being asked to participate in a research study to elicit energy drink consumer's knowledge of whether the ingredients of their Energy Drink (ED) interact with their prescribed psychiatric medications.

**Rationale:** This research is being conducted in order to contribute to the existing literature on energy drinks and their impact on the ED consumer. It is unique in that no other studies have yet been found that specifically seek to understand what consumers may know about possible ED ingredient interactions with their psychiatric medications. The information obtained may help in developing patient and prescriber education in regard to energy drinks.

**How you were chosen:** Your provider was asked to approach patients who they either: 1 - observed drinking ED's, or 2 - with whom they had previously discussed ED's, to inquire about their willingness to participate in this study. Your name and contact information as a possible subject was not provided to this researcher until you had specifically agreed to such.

**What to expect:** If you agree to participate in this study you will be asked to meet with this researcher for one face-to-face interview which consists of 5 questions. Anticipated length of interview will be ½ hour. You will be asked to supply a list of medications, vitamins, herbal preparations, supplements, and over-the-counter medications that you take. Participation is voluntary. You can choose to not answer any questions you do not want to answer and/or you can stop at any time.

**Risks:** There is a potential to experience concern or anxiety due to questions regarding one's health. As part of the participation agreement, you will be asked to schedule a post-interview appointment with your psychiatric provider. This researcher will also notify your provider of any possible concerns about ingredient interactions so you may discuss those concerns with your provider.

**Benefits:** There are no financial benefits to participating in this study. Developing awareness regarding your psychiatric medications may be of benefit to you.

**Source of funding:** This study has no funding.

**Cost to subject:** There is no cost to participate in this study.

**Confidentiality:** Strict confidentiality will be maintained. No specific patient identifiers (real names, date of birth, etc) will be used in the study write-up. The interview will be tape-recorded, then transcribed. Only this researcher will have access to the tapes and signed consent forms which will be kept in a locked cabinet for which only this

**APPROVED**  
**MSU IRB**  
**01/18/2017**

researcher has the key. The tapes and signed consent forms will be destroyed post-study, per Montana State University research protocols.

**Contact:** This research is being conducted by Anne McRae, a master's student at Montana State University. Ms. McRae can be contacted at [anne.mcrae1@msu.montana.edu](mailto:anne.mcrae1@msu.montana.edu) should you have any questions about the research. Additional questions about the rights of human subjects can be directed to the Chair of the Institutional Review Board, Mark Quinn, (406) 994-4707 [mquinn@montana.edu].

**APPROVED**

JAN 13 2017

**IRB OF BILLINGS**

**AUTHORIZATION:** I have read the above and understand the discomforts, inconvenience and risk of this study. I, \_\_\_\_\_ (*name of subject*), agree to participate in this research. I also agree to provide my medication list to be used by the researcher for the research study described in this consent form. I understand that I may later refuse to participate and that I may withdraw from the study at any time. I have received a copy of this consent form for my own records.

Signed: \_\_\_\_\_

Investigator: \_\_\_\_\_

Date: \_\_\_\_\_

Appendix B.2: Consent Form, Billings Institutional Review Board

IRB of Billings Protocol 17.07  
Authorization Form: Addendum to Consent  
IRB Review Date: 01-13-2017

Addendum to Consent Form: Privacy Authorization

**17.07 (MSU-Bozeman College of Nursing) Consumer's Knowledge of Energy Drink  
Ingredient Interaction With Their Prescribed Psychotropic Medications**

**Explanation and Background**

**Records – Use and Disclosure** This attachment to the information and consent form provides additional information about how your medical records and health information (together, your “records”) will be used and disclosed for this study. Your records may include information reviewed during the course of the study as described in the consent form. This form allows the researcher identified in the consent to use your records to carry out the study described in the consent form.

All of your records, the signed consent form(s), and this form also might be reviewed or copied by Montana State University, Billings Clinic, the Institutional Review Board (IRB) of Billings, or by other regulatory agencies in this country or in other countries. These agencies might review your records to check the information collected in this study, to check how the study was conducted or for other uses allowed by law.

**Possibility for Re-Disclosure** Federal and state laws require the researcher to protect the privacy of your records; however, absolute confidentiality cannot be guaranteed because of the need to disclose information as described above. In addition, after the researcher discloses your records to others, then the law may no longer protect the privacy of the information. If you would like to know how the university IRB will protect the privacy of your records, you can contact the university IRB at the telephone number listed in the consent form.

For questions about your rights as a research participant, contact the Institutional Review Board (IRB) of Billings, which is a volunteer group that acts as a research subject advocate. The IRB has reviewed this form for clarity of information. If you have any questions, comments, or concerns about this study or about your rights as a research subject, you may call the IRB at (406) 238-5657.

**Authorization Requirement for Participation** If you do not sign this authorization, you cannot participate in the study. You can cancel this authorization at any time by giving a written notice to the researcher. If you cancel this authorization, then you no longer will be able to participate in the study. The doctor may still use the information that has already been collected.

**Duration of Authorization** This authorization does not have an expiration date. If you do not cancel this authorization, then it will remain in effect indefinitely.

**Privacy Authorization** I authorize the release of my medical records and health information related to this study, including my signed consent form and this addendum, to Montana State University, Billings Clinic, the IRB of Billings, and other regulatory agencies as described above. By signing this form, I have not given up any of my legal rights as a research participant. I understand that I will receive a signed copy of this authorization for my records.

\_\_\_\_\_  
Printed Name of Participant

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date