"Designer drug- Trifluoromethylphenylpiperazine derivatives (TFMPP) - A future potential peril towards modern society

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Abstract:
"Designer drugs" (referred as synthetic drugs, research drugs/chemicals) are synthesized by drug dealers and chemists illicitly to elicit euphoric and psychostimulatory actions. These drugs are structural congeners of illegal and/or banned abusive substances and exhibit pharmacological effects similar to their parent drug. Moreover, due to its designed structural difference to circumvent drug laws, these can be currently obtained legitimately and readily in common stores and through internet. Alarmingly, several designer drugs are significantly toxic and perilous as compared to their corresponding street drug. Piperazine derivatives have been designed by substituting various chemical groups to the basic piperazine moiety to have a stimulatory effect. Various drugs with piperazine structural moieties are Benzylpiperazine-(BZP), 2C-B-BZP, CDPP, DBZP, MBZP, mCPP, MCDZP, MeOPP, pCPP, pFPP, and Trifluoromethylphenylpiperazine-(TFMPP). The most commonly abused piperazine derivatives are BZP, TFMPP and mCPP. But, there are few articles that have revealed the prevalence and toxic actions of TFMPP. Hence, in this review, we focus on pharmacodynamic, pharmacokinetic and toxic effects of TFMPP. Similar to other stimulants, TFMPP also increases the monoaminergic neurotransmission. Interestingly, TFMPP principally affects the serotonergic neurotransmission. TFMPP displays significant agonistic activity towards 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2C} receptors, except the 5-HT_{2A} receptor, where it acts as a weak partial agonist or antagonist. On the other hand, TFMPP has insignificant affinity towards 5-HT_3 receptor. It also affects release of acetylcholine and the release and uptake of monoaminergic neurotransmitters (dopamine, norepinephrine). Due to the specific effects of TFMPP on serotonergic neurotransmission, it induces hallucination, psychotropic effect, anxiety, nociceptic effect, hypothermia, hypotension, and bradycardia. Furthermore, it has a great impact on various behavioral activities such as aggression, avoidance, anxiety, sexual activities, feeding and accommodation. Conversely, if suitable prophylactic and therapeutic measures are not considered immediately, TFMPP can be an impending danger for the global health care.

Keywords:
- ✓ Trifluoromethylphenylpiperazine (TFMPP)
- ✓ Designer Drugs
- ✓ Substances of Abuse
- ✓ Psychostimulatory substances
- ✓ Serotonergic neurotransmission

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1. Global Drug Abuse:

According to the Oxford English Dictionary, the term "addict," refers to "attached by one's own inclination, self-addicted to a practice; devoted, given, inclined to". Campbell's psychiatric dictionary, describes addiction as "strong dependence, both physiologic and emotional". The term addiction has been used since the first part of the 16th century (1). Currently addiction is "state of being addicted to a substance / drug or action with a compulsion and need to continue". Addiction replaced older terms, such as habituation and inebriety. In addition, exposure to a substance can rapidly evolve from normal consumption, to abuse and then resulting in dependence. Physiologically, substances of abuse generally act on the dopaminergic neuronal tract (mesolimbic system) and glutamatergic pathway in the prefrontal cortex to induce pleasure and dependence respectively. Addiction leading to dependence and abuse has been well documented for several centuries. In Roman law, during the middle ages, addiction was the sentence pronounced against an insolvent debtor who was given over to a master to repay his debts with his work. Thus, addictus was a person enslaved because of unpaid debts. The issue of loss of control of the substance, heralding today's concept of addiction, was already being discussed in the 17th century. Substances that can have stimulatory potential leading to addiction were exploited by clerics of various religion and cultures, shamans for healing purposes and the common person for socialization. In the 18th century, opium's addictive potential was recognized when a large number of Chinese people became addicted, and the Chinese government tried to suppress its sale and use. In Europe, the working classes were threatened by alcoholism. Benjamin Rush, an American physician in the 18th century, observed that compulsive drinking was characterized by a loss of self-control, and that the disease was primarily attributable to the drink itself and not the drinker (2).

Drug abuse has plagued the American continent since the 1800s, when morphine, heroin and cocaine were hailed for their curative properties. The New York State Inebriate Asylum was the first hospital intended to solely treat alcoholism as a mental health condition was founded in 1864. In the late nineteenth century, several changes have occurred regarding new and exotic drugs, such as hallucinogens, amphetamines and marijuana, became more readily available. By the mid-20th century, however, the authorities tried to reduce/eliminate use of the illicit drug nationally and globally. Thus, for several centuries, people all over the world have used various substances repeatedly for their personal pleasure. During this period, there were always those who abused them, which led to full-blown addiction and the bevy of side effects that come with it. The origin of addiction medicine in modern times is sometimes credited to Calvinist theologians who offered explanations for the phenomenon of compulsive drinking, which were later accepted by physicians. Industrial revolution, international trade, were one of the reasons addiction became a global public health problem (3). Illegal drug traffickers were constantly looking for potent compounds and concoct faster routes of administration, which can contribute to very high levels of abuse. This ongoing vigorous search for new substances of abuse, psychoactive substances and recreational drugs, resulted in the concept of modern "Designer drugs". Designer drugs are usually synthetically prepared in the clandestine labs to elicit addictive effects comparable to banned or illegal addictive substances. These drugs are usually structural analogues of a known substance of abuse / controlled substance. Initially, designer drugs were not classified under the controlled substance. 3-Trifluoromethylphenylpiperazine

(TFMPP) is a well-known designer drug that is being abused throughout the world. However, there are very few reports regarding the toxic effects and the possible therapeutic strategies to overcome the abuse potential and adverse effects associated with TFMPP-induced dependence. Hence, in the review, we focus on the pharmacokinetic, pharmacodynamic and adverse effects associated with TFMPP.

2. TFMPP- Designer Drug:

Trifluoromethylphenylpiperazine (TFMPP) is a schedule I controlled substance of abuse which is a member of the piperazine chemical class of designer drugs. Piperazine designer drugs emerged in the drug market for recreational purposes with psychoactive properties. Substituting different functional groups onto the basic piperazine structure creates derivatives such as benzylpiperazine (BZP or 1-benzylpiperazine) and trifluoromethylphenyl-piperazine (TFMPP). BZP is a benzyl substituted piperazine, while TFMPP is a substituted phenyl amine (Figure 1). TFMPP is most commonly consumed with benzylpiperazine or ecstasy to give psychostimulatory effects similar to illegal or banned drugs such as morphine, heroine, methamphetamine, MDMA, ecstasy. TFMPP has been associated with various street names including "X4" and numerous brand names relating to its availability as a perceived legal "Ecstasy" alternative (e.g. "PEP", "Twisted", "Flying Angel" and "Wicked High").

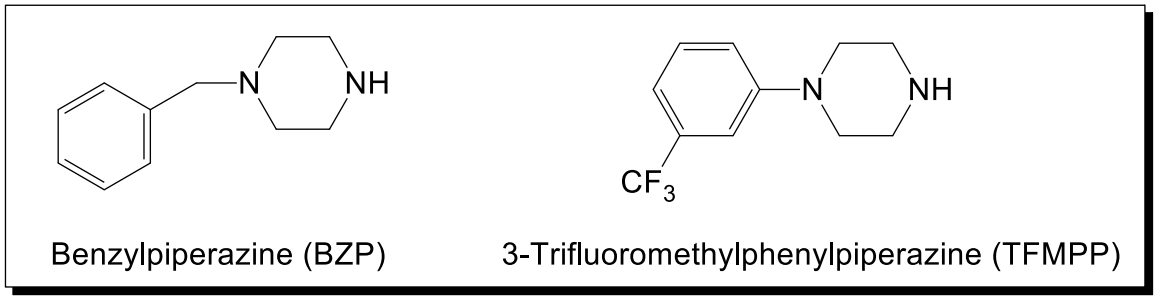

Figure 1

Initially, piperazine derivatives were designed to be used as anti-helminthic. The anti-helminthic effect may be due to the blockade of the neuromuscular transmission in the parasite by hyperpolarizing the nerve membrane, which causes flaccid paralysis. Piperazine derivatives also blocks succinate production in the worm which leads to energy depletion. The mode of action of antihelminths is to basically cause interference with the integrity of parasite cells, neuromuscular coordination, or protective mechanisms against host immunity, which lead to starvation, paralysis, and expulsion or digestion of the parasite. In 1999, Japanese scientists discovered N-benzylpiperazine to stimulate the production of acetylcholine. Increased cholinergic neurotransmission in the Central Nervous System (CNS) is associated with enhanced learning and memory. This conceptual scientific intervention provided in part the rationale for the design and synthesis of Donepezil, a substituted piperidine derivative of BZP (Figure 2) that inhibits acetylcholinesterase. Donepezil is the current first line of therapy in the treatment of Alzheimer's disease and other age-related dementias, or brain diseases associated with progressive loss of memory, learning, and thinking ability.

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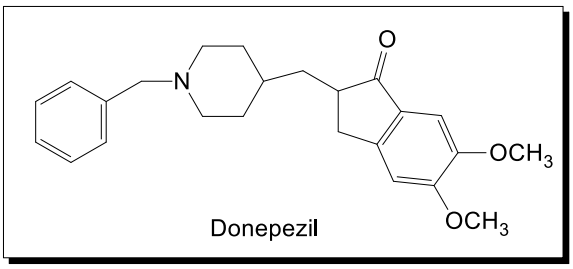

Figure 2

In the 1970s, TFMPP was found to be a metabolite of antrafenine, an analgesic anti-inflammatory medicine comparable to naproxen. During metabolism studies, it was suggested that due to its serotonergic effects, TFMPP may be partly responsible for its activity (Figure 3). However, while there have been a number of studies investigating the therapeutic potential of TFMPP as well as BZP, these drugs have not demonstrated significant efficacy or safety in the treatment of disease. Currently TFMPP is not listed on the WHO Model List of Essential Medicines and has never been marketed as a drug.

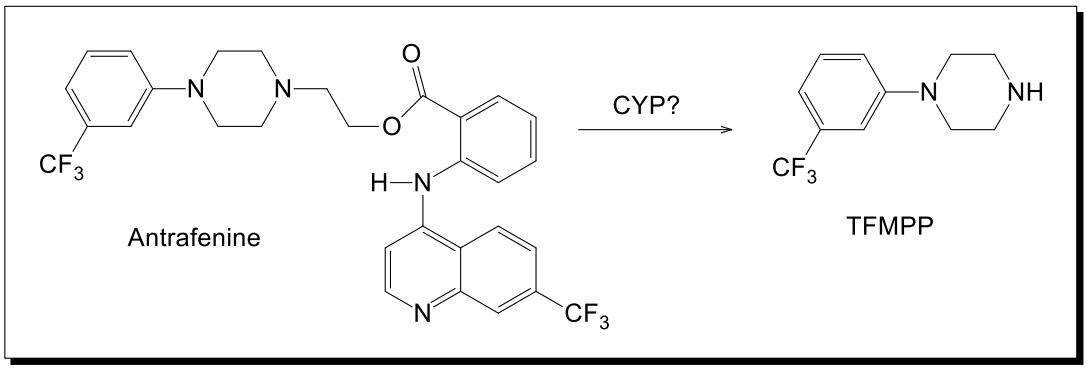

Figure 3

In fact, there are serious adverse effects due to the consumption of TFMPP as described in the sections that follow. As of 2002, two deaths have been reported due to toxic effects of TFMPP and many more cases of non-fatal intoxication. In the United States, TFMPP was temporarily classified under Schedule I due to concerns about toxicity and abuse potential, along with the lack of clear medical application. However, in 2002, based on the scientific and medical evaluation conducted by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), the Department of Health and Human Services (DHHS) did not recommend further control, leaving TFMPP as a federally uncontrolled substance after March of 2004. Since then there has been an escalation in the abuse of TFMPP in the United States as evidenced by the increasing encounters of this substance by law enforcement officials in various states. This prompted some states

such as Florida that have banned the drug in their criminal statutes making its possession a felony. In New Zealand, BZP and TFMPP were initially classified under Schedule IV of the Misuse of Drugs Amendment Act 2005 (Amendment to the Misuse of Drugs Act 1975) as restricted compounds, available for legal sale to any person aged over 18 years. The sale of TFMPP is also controlled in Canada, China, Denmark, Japan, Sweden, Belgium, Greece the United Kingdom and Australia. There are numerous studies over the past two decades that has revealed the abuse of TFMPP around the world (4–20).

2.1: **TFMPP- a valid pharmacological tool for research purpose:**

Prior to the abuse of TFMPP, it was used by numerous scientists as a valid pharmacological tool for research purpose. TFMPP was used for the following research purposes (21,76):

- ✓ Evaluate the role of monoamines in Addiction (21,22)
- ✓ Study of Aggressive actions (23,24)
- ✓ Role of monoamines and hormones in Anorexia (25,26)
- ✓ Anxiogenic mechanisms (27)
- ✓ Establish the effect of monoamines on various General Behavior:
  - Chewing (28,29)
  - Discriminative stimulus (30,31)
  - Exploratory activities (32,33)
  - Head twitch effects (34,35)
  - Learning abilities (36–38)
  - Locomotor ability (movement) (39)
  - Memory formation (40, 63)
  - Operant behavior (41,42)
  - Psychoactive behavior (8)
  - Social behavior (43,44)
  - Stimulatory effect (45)
- ✓ Regulation of monoamine in Body temperature (46,47)
- ✓ Role of serotonin in regulating Cardiovascular function (52)
- ✓ Cell signaling pathway (45)
- ✓ Serotonergic mechanisms in Circadian rhythm (48)
- ✓ Influence of monoamine in Convulsion (49,50)
- ✓ Consequences of monoamines and hormones in Depression (51,52)
- ✓ Understand Drug-Receptor ligand binding (53,54)
- ✓ Role of monoamine in Emesis (55,56)
- ✓ Establish Endocrine function (Glucagon, Glucose, Insulin, Neuropeptide-Y, Somatostatin, Androgen, pituitary hormone) (57,58)
- ✓ Feeding behavior (59,60)
- ✓ Hypersensitivity reactions (61)
- ✓ Lordosis (62)
- ✓ Meiosis reinitiation
- ✓ Melatonin production (64)
- ✓ Mechanisms involved in Neuronal firing (65)
- ✓ Nociception mechanisms (66)
- ✓ Understand Pain pathway (21)
- ✓ Receptor stimulation / inhibition and its function (67)

- ✓ Reflex responses
- ✓ Release of Neurotransmitters mechanisms (69)
- ✓ Respiratory function (70,71)
- ✓ Reward pathway (72)
- ✓ Sexual Behavior (73)
- ✓ Sleep wake cycle (74)
- ✓ Synaptic Neurotransmission (69, 75)
- ✓ Synthesis of Neurotransmitters (76)

3. Pharmacokinetic effects of TFMPP:

TFMPP is typically obtained in the form of a powder, tablet or capsule and the primary route of administration is oral as reported by users. However, there are also reports of the drug being "snorted" or smoked, which have been noted for BZP and other piperazines and even injected. It is presumed that smoking and parenteral administration (injection) delivers substances of abuse to the CNS more rapidly, resulting in addiction as compared to other routes such as swallowing, which deliver the drugs more slowly. With regard to TFMPP, the plasma concentrations following a single 60mg oral dose in humans peaked at 24ng/mL (Tmax = 90 minutes). TFMPP had two disposition phases with calculated half-lives of 2 hours and 6 hours, with Cl/F of 384 L/hour. A single plasma metabolite, 4-OH TFMPP (C Max = 20 ng/mL; Tmax = 90 min), was detected in this study (77). Urinary metabolites included 4-OH TFMPP and an N-glucuronide of TFMPP, with some evidence of conjugates of 4-OH TFMPP (77). A more detailed analysis of TFMPP metabolism is presented below.

TFMPP, due to its structure, readily crosses the blood brain barrier. A positive relationship has been reported between plasma drug concentrations and subjective ratings indicating that TFMPP have concentration-dependent subjective effects (78). These findings suggest that elevated concentrations of these drugs (due to compromised clearance or larger doses) may result in elevated effects on mood (79). A study of the tissue distribution of BZP and TFMPP has also noted a significant difference in the extent of distribution of these drugs in the rat (80). The organ with the highest concentration of BZP was the kidneys with a concentration ratio between the plasma and kidneys of approximately 1:20, while the TFMPP concentration ratio between the plasma and the lungs (organ with the highest TFMPP concentration) has a ten-fold difference at approximately 1:200, thirty minutes after the dose. This study reported that the ratios of BZP and TFMPP between plasma and all other analyzed tissue (brain, liver, kidneys, lungs, heart) were 1:40 and 1:385 respectively, thirty minutes after the dose. Therefore, the presence of a more obvious distribution phase in the human plasma profile of TFMPP when compared to BZP is in agreement with tissue distribution data from the rat (80). As TFMPP does not persist in plasma for longer than 24 hours, these results also suggest that subjective effects of these drugs should last no longer than 24 hours at the given dose. However, it is important to note that the drug effects are not the same for every individual, with a minority demonstrating the opposite relationship between concentration and effect. Conversely, reports from animal studies have indicated that the subjective effects of these drugs are synergized when they are co-administered (81). This suggests that the interaction resulting in synergism between these drugs occurs at a pharmacodynamic level. This further suggests that by combining BZP and

TFMPP, the doses of each can be reduced without compromising the effect of the drugs which may explain why, when these drugs are sold in combined drug preparations, the doses of each drug are routinely far lower than in the single drug preparations. Interestingly, combining TFMPP with caffeine also resulted in lethal consequences due to pharmacokinetic interactions of elevated caffeine concentrations (82–84).

Initially, the metabolism of TFMPP in rodents provided insight into probable routes for their metabolism in humans (85). By administering inhibitors quinidine, furafylline and troleandomycin it was found that CYP2D6, CYP1A2 and CYP3A4 metabolize TFMPP. CYP2D6 poor metabolizers have compromised metabolism of TFMPP both *in vitro* and *in vivo*. CYP2D1 (the rat orthologue of human CYP2D6) was claimed to be the principle enzyme responsible for the metabolism of TFMPP, accounting for 80.9 % of TFMPP metabolism in rats. CYP1A2 and CYP3A4 also contributed to the metabolism, but to a lesser extent, 11.5% and 7.6 % respectively. It was proposed that TFMPP metabolism occurs via hydroxylation of the phenyl group and to a lesser extent, dealkylation of the piperazine ring. Subsequent degradation, acetylation and conjugation (glucuronation and sulfonation) can result in a number of metabolites (85). Later it was found that TFMPP is metabolized by CYP2D6, CYP1A2 and CYP3A4 in the human liver (79). However, these enzymes have different affinities for TFMPP and its structural congeners like BZP. The metabolism of TFMPP has been shown to be diminished by the presence of the inhibitors of these enzymes and other substrates. An important concern is that of compromised metabolism of TFMPP in 'poor metabolizers' can have a serious clinical interaction with antidepressants (paroxetine), atypical antipsychotics (olanzapine) and Antiepileptics (Carbamazepine). Previous studies with male Wistar rats (WI) had shown that TFMPP was metabolized mainly by aromatic hydroxylation. In another study, it was examined role of CYP2D6 on TFMPP. These investigators measured and compared TFMPP vs. hydroxy TFMPP ratios in urine from female Dark Agouti rats. Dark Agouti rats are a well-accepted animal model to study the CYP metabolism of the human. Male Dark Agouti rats are of the poor CYP2D6 metabolizer phenotype (PM) and WI is a model of the human CYP2D6 extensive metabolizer phenotype. Analysis of the plasma samples showed that female Dark Agouti rats exhibited significantly higher TFMPP plasma levels compared to those of male Dark Agouti rats and WI. Furthermore, pretreatment of WI with the CYP2D inhibitor quinine resulted in significantly higher TFMPP plasma levels (85–88). The identified metabolites indicated that TFMPP was extensively metabolized, mainly by hydroxylation of the aromatic ring and by degradation of the piperazine moiety to N-(3-trifluoromethylphenyl) ethylenediamine, N-(hydroxy-3-trifluoromethylphenyl) ethylenediamine, 3-trifluoromethylaniline, and hydroxy-3-trifluoromethylaniline (Figure 4). Phase II reactions included glucuronidation, sulfatation and acetylation of phase I metabolites (87). Furthermore, the human hepatic CYPs involved in TFMPP hydroxylation were identified using cDNA-expressed CYPs and human liver microsomes. The urine studies suggested that TFMPP hydroxylation might be catalyzed by CYP2D6 in humans. Studies using human CYPs showed that CYP1A2, CYP2D6 and CYP3A4 catalyzed TFMPP hydroxylation, with CYP2D6 being the most important enzyme accounting for about 81% of the net intrinsic clearance, calculated using the relative activity factor approach. The hydroxylation was significantly inhibited by quinidine (77%) and metabolite formation in

poor metabolizer genotype human liver microsomes was significantly lower (63%) compared to pooled human liver microsomes.

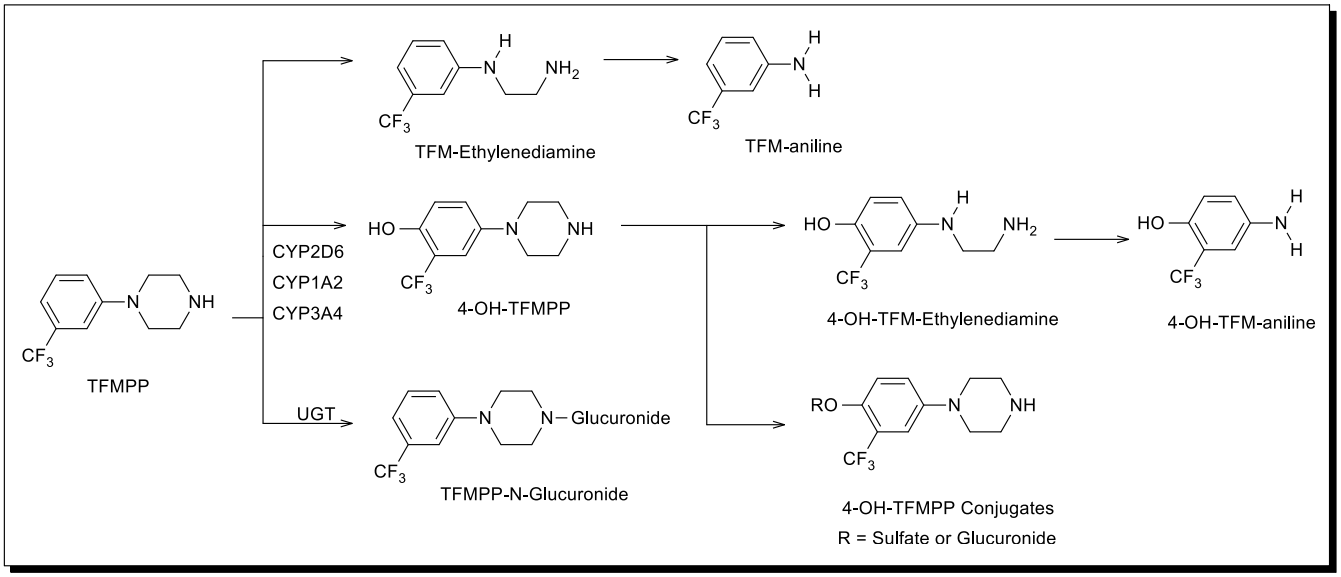

Figure 4

4. Pharmacodynamic actions of TFMPP:

The pharmacodynamic effects of TFMPP result from its effects on monoaminergic neurotransmitters in particular serotonin (5-HT). TFMPP also affects other monoaminergic neurotransmitters dopamine (DA), and noradrenaline (NA). TFMPP has significant affinity towards 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, and 5-HT_{2C} receptors. TFMPP exhibits agonistic activity (binds with intrinsic effect) at all sites except the 5-HT_{2A} receptor, where it acts as a weak partial agonist or antagonist. Interestingly, TFMPP has insignificant affinity for the 5-HT_3 receptor (68,81).

Since the receptors for monoaminergic neurotransmitters are present in both the central and peripheral nervous system (PNS), TFMPP can have significant effects in both brain and periphery. The primary mechanisms associated with increased serotonergic neurotransmission may be due to its ability to bind with post-synaptic serotonergic receptors resulting in agonist activity (89,90) even though TFMPP exhibits both agonists and antagonistic effects on the serotonin receptors. In the CNS, it acts as a 5-HT agonist that results in neuroendocrine action, behavioral and serotonin turnover effects but in the periphery it exhibited potent antagonistic effect leading to serotonin-induced contraction of the jugular vein (91). Similar to TFMPP, quipazine (a piperazine derivative) and Org 10155 also exhibited 5-HT agonistic activity and were sensitive to calcium entry blockade (52). In addition to the effect on postsynaptic 5-HT receptors, TFMPP also can enhance the release of serotonin. When tested on rodent hypothalamic slices (*in vitro*), piperazines can induce a significant release of 5-HT, and this effect must be taken into account for their serotonergic pharmacological action in

addition to its direct agonist activity when understanding the *in vivo* CNS effects of TFMPP (92–94). With regard to the serotonergic release, the action may be attributed to the effect of TFMPP on 5-HT_1 and 5-HT_{1B} receptors (54,60,74,95–99). The effect of TFMPP of serotonergic neurotransmission translates towards many actions in the body. Due to the effect on 5-HT neurotransmission, it induces hallucination, psychotropic, anxiogenic, nociceptic effect, hypothermia, and affects rapid-eye-movement (REM) sleep, exploratory activity and release of other neurotransmitters.

Hallucinogenic effects of TFMPP may be due to its effect on serotonergic receptor (100). In general, the hallucinogenic effects are more prominent due to the stimulation of 5-HT_2 receptor. With regard to the effect of TFMPP on rapid-eye-movement, it has shown that it causes suppression of rapid-eye-movement (REM) sleep. TFMPP (single injection) in rodents induced a substantial, dose dependent short-term (4-5h) suppression of rapid-eye-movement (REM) sleep. TFMPP augmented non-REM (NREM) sleep during the second hour. This study further confirms that suppression of REM sleep is due to its effect on the central serotonergic neurotransmission (74). Hypothermia can result in a health emergency due to the fall in the body temperature below 95^{o}F (35^{o}C). TFMPP induces hypothermia in rats by binding at 5-HT_{1B} receptors (101). Interestingly TFMPP's ability to cause hypothermia was confirmed by another study where it they also showed that a lower dose of TFMPP evoked a hyperthermic and the higher a hypothermic response (46). Due to its effect on 5-HT_{1B} receptors, TFMPP also possess psychotropic activity similar to imipramine and its derivatives (102). Nociception occurs due to the activation of nociceptors that leads to the processing of information about the internal or external environment in the peripheral and central nervous system. An injury can stimulate nociceptors that are present in the periphery that triggers signals to the spinal cord dorsal horn or its trigeminal homologue, the nucleus caudalis. TFMPP due to its serotonergic stimulatory effect has anti-nociceptive effects (103).

Exploratory behavior of laboratory rodents is of significance to understand the behavioral pharmacology of humans. A rodent introduced to an unfamiliar settings or entity displays behavioral changes that is referred to as exploration. The exploratory activity can be referred to the movement around an environment, positioning/adjusting towards a novel object, exploring (touching or sniffing) a new and /or novel objects (104–106). The exploratory activity offers innovative evidence about various behavioral activities associated with feeding, accommodations and sexual activities. Introducing an animal to a new environment or exposing to a novel stimulus, escalates its risk of predation, aggression from conspecifics or other hazards (107,108). Neophilia and neophobia are behavioral concepts that explain the curiosity-based approach to, and fear-based avoidance of, a novel stimulus (109). Neophilia is the attraction exhibited by an animal towards a novel object by an animal while neophobia is the act of displaying aversion (108). Neophilia is related to the neuronal functions associated with the rewarding effects of addiction / abuse (110). The most regularly used behavioral tests associated with exploratory behavior are the open field (111–113). The pharmacological mechanism associated with the exploratory activity in this model is due to the activation of 5-HT_{1C}, or 5-HT_{1B}, receptors (39). TFMPP and m-CPP-induce a decrease in the exploratory activity (114). TFMPP also decreased the total interaction time in a rat social interaction test. The total social interactions test takes into the

consideration the following behavior: grooming, following, crawling over, fighting and sniffing. The results from the study reveal that TFMPP has an anxiogenic effect without the sedative action (60). There was another study that confirmed the above behavioral effect where TFMPP-increased conditioned avoidance response and this action was also attributed to the action on the $5HT_{1C}$/5-HT_2 receptors (115).

Serotonin has shown to affect the release of other neurotransmitters including norepinephrine, dopamine and acetylcholine. Serotonin is mainly synthesized in the rostral, median and caudal raphe complex (perikarya, cell body, in the CNS) and the enterochromaffin cells in the PNS. The serotonergic neuronal tracts from the rostral raphe complex neurons project to the forebrain, while those from the caudal raphe complex neurons project to the brainstem and spinal cord. The serotonergic neuronal tracts from the median raphe and dorsal raphe nuclei neuros provide parallel and overlapping projections to many forebrain regions. These neuronal tracts then regulate the release of other neurotransmitters in the regions to which they project. Therefore, since TFMPP affects serotonergic neurotransmission it can have a significant influence on the release of other neurotransmitters. The effect on the release of other neurotransmitters may be due to inhibiting synaptic potentials in the serotonergic perikarya-locus ceruleus and its prominent effect on the terminal axons of serotonergic neurons (116,117). TFMPP also has been shown to inhibit the K+-evoked release of acetylcholine from rat hippocampal synaptosomes (118) and induce in vitro and in vivo dose-dependent extracellular dopamine release (119). TFMPP increased dopamine release in the substantia nigra, striatum and limbic forebrain and this was confirmed by the accumulation of dopamine metabolite 3-MT (120). In the ventral tegmental area, TFMPP showed maximal inhibition of the basal activity of dopamine neurons (121). TFMPP also decrease epinephrine content in rat hypothalamus (122). These findings exhibit TFMPP and MDMA share the ability to evoke monoamine release, and dangerous drug-drug synergism may occur when piperazines are co-administered at high doses (81).

With regard to other behavioral activity, TFMPP has shown been shown to suppress aggression in rats (123), and to facilitates lordosis in 5,7-DHT-treated and non-treated rats (62). Lordosis is the normal inward lordotic curvature of the lumbar and cervical regions of the human spine. TFMPP amplified vacuous chewing movements (29) and induced inhibition of saccharin taste preference (124). TFMPP attenuated posthypoxic myoclonus (75). Serotonin controls the phase adjusting effects of light on the mammalian circadian clock through the activation of presynaptic 5-HT_{1b} receptors located on retinal terminals in the suprachiasmatic nucleus (SCN). TFMPP also attenuated the inhibitory effect of light on pineal melatonin synthesis in a dose-related manner (64). Finally TFMPP also reduces the frequency of pilocarpine-induced epilepsy in rats (49).

4.1. TFMPP on the Peripheral Nervous System:

With regard to its actions in the periphery, TFMPP can modify the function of a host of tissues including those of the ophthalmic, cardiovascular, respiratory, gastrointestinal, urinary, reproductive and endocrine systems. In the eye, TFMPP acts on the presynaptic 5-HT_{1B} receptors, of the retinal terminals in the suprachiasmatic nucleus and this activation of these receptors by TFMPP inhibits retinohypothalamic input (48). TFMPP

displays a pharmacological profile comparable to a serotonergic agonist on the cardiovascular system. Multiple studies have demonstrated that TFMPP administration produces a dose-dependent hypotension and bradycardia (71,91,97). TFMPP causes contractions of uterine arteries and also umbilical veins and arteries from fetal lambs (125). In the respiratory tract, the effect of TFMPP was similar to the activation of 5-HT_{1A}, 5-HT_{1B} and 5-HT_2 receptor subtypes at the intermediate area of the ventral surface of the medulla. TFMPP affects the laryngeal and phrenic nerve. The phrenic nerve originates in the neck and descends through the thorax to reach the diaphragm. It is associated with the motor innervation of the diaphragm and helps regulate breathing. The larynx, under control of the laryngeal nerve, regulates respiration, and aids in airway protection, coordination of swallowing, and phonation. TFMPP has been shown to reduce the d-amplitude of the recurrent laryngeal and phrenic nerve signals (71). Furthermore, TFMPP by acting on the 5-HT_{1B} receptors decreases the respiratory activity, increase pulmonary resistance and decrease in dynamic lung compliance (70). TFMPP also affects the pharynx by increasing the basal tone and affects phasic contractions (126).

In the gastrointestinal tract, TFMPP causes hypophagia by interaction with 5-HT_{1B} receptors (127). Hypophagia refers to the suppression of caloric intake due to the reduction in feeding due to administration of drugs surgery or environmental interventions (such as change in diet). The hypophagic effect may be due to the effect of TFMPP on the paraventricular nucleus of the hypothalamus. TFMPP induces anorexia by interacting with 5-HT_2 and 5-HT_{1C} receptors. TFMPP causes relaxation of smooth muscle-anterior byssus retractor muscle of Mytilus (99). With regard to the effect on sexual behavior, TFMPP exerts mixed actions. TFMPP reduces the rodent's sexual masculine behavior as it reduces the copulation of animals (128). However, (129) showed that TFMPP induced penile erection at $5HT_{1C}$ receptors. TFMPP also affects the hormonal secretion and affects the endocrine functions which may impact on sexual behavior. The actions of TFMPP on the endocrine system are complex. There are various studies that demonstrate an effect of TFMPP on the glucose level. Pretreatment with 1-(3-chlorophenyl)-piperazine (mCPP) or TFMPP decreased 2,5-Dimethoxy-4-iodoamphetamine-induced hyperglycemia in a dose-dependent manner (130). TFMPP also has been shown to affect insulin level without disrupting glucose homeostasis (58). TFMPP can promote the release of adrenocorticotropin (ACTH) and increase serum corticosterone levels. It also can increase prolactin levels and promote the release of arginine vasopressin (AVP) into the portal vessels from the anterior pituitary via the central serotonergic mechanism (131). Finally there were studies showing that TFMPP acts additively with BZP to produce significant hepatotoxicity. *In vitro* hepatotoxicity of 'Legal X': the combination of BZP and TFMPP triggers oxidative stress, mitochondrial impairment and apoptosis (76,132). Piperazine designer drugs have also been shown to affect cholesterol biosynthesis and escalates the risk of phospholipidosis and steatosis (133). The compiled pharmacodynamic actions attributed towards serotonergic neurotransmission of TFMPP are given in Table 1.

5. Toxicological effects and Identifications of TFMPP:

TFMPP may be an ingredient in clandestine drug products marketed as ecstasy and BZP, or and abusers hoping for an extended or intensified "high" from ecstasy sometimes deliberately combine these drugs. The median consumption of TFMPP is 400 mg but can

range from 43-2500 mg. In humans, combined BZP and TFMPP (mean quantity) consumed on an incident of utmost use has been reported to be 533 mg. TFMPP has shown to induce bradycardia and reduce the rate of breathing, impair the ability to move and to regulate of body temperature. This results in high fevers that cannot be reversed, leading to heart, liver and kidney failure. The other general adverse effects are insomnia, anxiety, nausea, vomiting, headache, migraine, seizures, impotence, psychosis interference with circadian system and hypophagia. In New Zealand toxic seizures and respiratory acidosis has been reported in several patients. As of 2002, there had been two reported deaths from BZP/TFMPP. The mechanisms of toxicity may be due to its effect on the serotonergic neurotransmission and endocrine function. In the cellular level, TFMPP decreases intracellular ATP, accompanied by increased intracellular calcium levels, reactive oxygens species, depletion of antioxidants and a decrease in mitochondrial membrane potential that seems to involve the mitochondrial permeability transition pore. The cell death mode revealed early apoptotic cells and high number of cells undergoing secondary necrosis (132–135). TFMPP also increases the biosynthesis of cholesterol by acting on the synthesizing enzymes and potentiate the risk of phospholipidosis and steatosis (133). Like any other stimulants, TFMPP also increases the monoaminergic neurotransmission and inhibits the GABAergic inhibitory neurotransmission. TFMPP exhibits antagonistic effect on the GABA-A receptor which leads to increased monoaminergic neurotransmission resulting overdoses (136). Among the tested drugs, TFMPP seems to be the most potent cytotoxic compound. Overall, piperazine designer drugs are potentially cardiotoxic, supporting concerns about the risks associated with abuse of this drug class. Finally the toxic effects of TFMPP and TFMPP-containing drugs of abuse are more prominent in females as compared to the males. Females may be at greater risk of experiencing toxicity from BZP/TFMPP party pills due to their smaller physical size and therefore greater exposure. Furthermore, consuming enormous amounts of TFMPP-containing drug products in a single party setting and concurrently with cannabis, BZP and 5-hydroxytryptophan (5-HTP) recovery pills definitely has shown to increase detrimental toxic effects in both males and females, presumably due to the ability of all of these substances to potentiate serotonin release (18). A number of methods for the identification and quantification of 3-TFMPP in body fluids have been published (15,72,86,137–154). Most of these rely either on gas chromatography with mass spectrometry (GC/MS) or liquid chromatography coupled with mass spectrometry (LC/MS). In most MS analyses TFMPP shows the expected molecular ion at 230 mass units and gives other characteristic ions at m/z of 188, 174, 173,172 and 145 arising from fragmentation of the piperazine ring. More recently (155) has published a method to differentiate 3-TFMPP from its 2- and 4-TFMPP regioisomers using GC-MS and GC-IRD.

6. Conclusion:

TFMPP is an incipient psychoactive designer drug, whose abuse is engaged for stimulating and recreational activities worldwide. As with other drugs of abuse, TFMPP acts predominantly on monoaminergic neurotransmission, thus causing psychostimulatory effects. Abuse of TFMPP has led to increased mortality and morbidity. Few studies have investigated the potential risks and mechanisms of toxicity associated with TFMPP. Clinical investigations into the abuse of TFMPP are much required because these drugs are available easily in many countries, stores and online. Consequently,

there is an urgent need for detailed research to identify and quantify the drugs in various formulations and elucidate the cellular and molecular toxic effects of these new designer drugs of abuse.

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"Designer drug- Trifluoromethylphenylpiperazine derivatives (TFMPP) - A future potential peril towards modern society

Table-1: Actions of TFMPP:

<table>
<tr><th>Organs</th><th>Action of TFMPP</th></tr>
<tr><td>CNS</td><td>

Increases serotonergic neurotransmission
Release ACTH from the anterior pituitary
Release arginine vasopressin (AVP) from posterior pituitary
Thermoregulation: lower dose of TFMPP evokes hyperthermic response and high dose hypothermic response
Affects Mood and Behavior: Hallucinogenic, psychotropic, anxiogenic effects
Anti-nociceptive properties
Modulates release of other neurotransmission serotonin, dopamine, and noradrenaline
Involved in sleep regulation: suppression of REM sleep, augmentation of NREM sleep
Facilitate lordosis
Regulation of nocturnal pineal melatonin production: Attenuated the inhibitory effect of light on pineal melatonin synthesis

<table>
<tr><td>$5HT_{1A}$</td><td>agonist</td><td>Affects respiratory function</td></tr>
<tr><td>$5HT_{1B}$</td><td>agonist</td><td>Affects release of neurotransmitters
Hypothermia
Psychotropic effect
Exploratory activity
Circadian rhythm
Depresses respiratory activity
Hypophagia
Controls behavior</td></tr>
<tr><td>$5HT_{1C}$</td><td>agonist/antagonist</td><td>Decreases anorexia</td></tr>
<tr><td>$5HT_{1D}$</td><td>agonist</td><td></td></tr>
<tr><td>$5HT_{2A}$</td><td>partial agonist/antagonist</td><td>Psychosis
Avoidance
Exploratory activity</td></tr>
<tr><td>$5HT_{2C}$</td><td>agonist</td><td>Hallucinogenic
Exploratory activity
Avoidance
Hypophagia
Suppression of REM</td></tr>
</table>
</td></tr>
<tr><td>EYE</td><td>Inhibits retino-hypothalamic input</td></tr>
<tr><td>CVS</td><td>Decrease in blood pressure and heart rate</td></tr>
<tr><td>Respiratory Tract</td><td>Decreases respiratory activity
Increase in pulmonary resistance and decrease in dynamic lung compliance</td></tr>
<tr><td>Gastrointestinal Tract</td><td>Hypohagia
Anorexia</td></tr>
<tr><td>Urinary Tract</td><td>Hyponatremia
Acute urinary retention
Acute tubular necrosis</td></tr>
<tr><td>Reproductive system</td><td>Reduces sexual masculine behavior
Contraction of uterine arteries</td></tr>
<tr><td>Endocrine system</td><td>Induces hyperglycemia
Increases serum corticosterone and prolactin</td></tr>
<tr><td>Immune system</td><td>Suppresses Delayed Hypersensitivity response</td></tr>
</table>