Zacks Small-Cap Research

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Tonix Pharmaceuticals Holding Corp. (TNXP-NASDAQ)

TNXP: A Closer Look at the Use of MDMA for the Treatment of PTSD…

Based on our probability adjusted DCF model that takes into account potential future revenues from TNX-102 SL PTSD, TNXP is valued at $2/share. This model is highly dependent upon continued clinical success of TNX-102 SL in PTSD and will be adjusted accordingly based upon future clinical results.

Current Price (12/14/16)	$0.45
Valuation	**$2.00**

OUTLOOK

There have been a number of reports in the media recently on the use of 3,4-methylenedioxymethamphetamine (MDMA), commonly known as ecstasy, as a treatment for posttraumatic stress disorder (PTSD) when used in combination with psychotherapy. While the use of MDMA for treating PTSD has brought much needed attention to a group of patients who have few treatment options available, we foresee a number of serious impediments to advancing MDMA as a feasible pharmacotherapy for a large number of PTSD patients. Tonix will be initiating a Phase 3 program in PTSD with TNX-102 SL in the first quarter of 2017, and we continue to believe that Tonix is the leading developer of a potential pharmacological PTSD treatment.

SUMMARY DATA

52-Week High	**$7.79**
52-Week Low	**$0.37**
One-Year Return (%)	**-93.48**
Beta	**2.85**
Average Daily Volume (sh)	**1,475,692**
Shares Outstanding (mil)	**39**
Market Capitalization ($mil)	**$18**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**10**
Insider Ownership (%)	**10**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Value**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	0 A	0 A	0 A	0 A	0 A
2016	0 A	0 A	0 A	0 E	0 E
2017					0 E
2018					0 E

Earnings per Share
(EPS is operating earnings before non recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	-$0.71 A	-$0.73 A	-$0.72 A	-$0.71 A	-$2.86 A
2016	-$0.74 A	-$0.50 A	-$0.29 A	-$0.19 E	-$1.52 E
2017					-$0.56 E
2018					-$0.57 E

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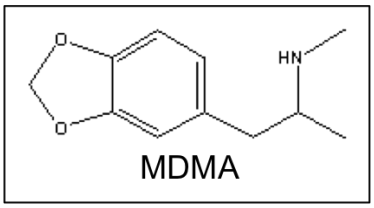
MDMA Being Developed for the Treatment of PTSD

A number of recent articles (see here for an example) have highlighted the potential for using 3,4-methylenedioxymethamphetamine (MDMA), commonly known as ecstasy, as a treatment for posttraumatic stress disorder (PTSD) when used in combination with psychotherapy. Since we believe investors interested in Tonix Pharmaceuticals may not be aware of the work being performed with MDMA in PTSD, we have examined the opportunity and provide a summary below.

The Multidisciplinary Association for Psychedelic Studies (MAPS) has recently completed Phase 2 testing of MDMA in veterans with PTSD. In addition, the FDA has agreed to a Phase 3 trial protocol, which is likely to get underway in 2017. While this news has generated an appreciable amount of "buzz" in the press, particularly since MDMA may have some utility in the treatment of PTSD, we don't believe that MDMA will likely ever have broad acceptance or gain appreciable market share due to a number of confounding factors associated with its use. Below we provide investors some background on MDMA and its use in treating PTSD patients, along with why we think it is unlikely to attain widespread use in the treatment of PTSD.

MDMA



MDMA

MDMA, which is most commonly known as ecstasy, is a psychoactive drug primarily used recreationally. When taken orally, users describe feelings of increased empathy, euphoria, and heightened sensations. These effects typically begin 30-45 minutes following administration and continue for three to six hours. Side effects from the use of MDMA include nausea, chills, sweating, muscle cramping, and dehydration. MDMA overdose is marked by high blood pressure, faintness, panic attacks, and the potential for loss of consciousness and seizures.

German scientists at Merck first synthesized MDMA in 1912, however the first pharmacological tests did not occur until 1927 and toxicological tests were not conducted until the 1950's (Bernschneider-Reif *et al*., 2006). The first scientific publication on the synthesis of MDMA was not published until 1960. The drug began being used recreationally by the late 1970's, and although many psychiatrists, psychotherapists, and researchers objected, the drug was classified a Schedule I drug by the U.S. Drug Enforcement Agency (DEA) in 1985. Being Schedule I means a drug has a high potential for abuse, has no currently accepted medical use in the U.S., and there is a lack of accepted safety for use under medical supervision.

Use in Psychotherapy

Due to its potential to evoke feelings of euphoria and life-affirming effects, the use of MDMA as an adjunct to psychotherapy was first proposed in the late 1970's. One of the earliest descriptions of the use of MDMA in a therapeutic setting was in the mid 1980's (Greer *et al*., 1986). Twenty-nine individuals, none of whom had any severe psychological problems, were administered 75-150 mg of MDMA prior to therapy sessions, which typically took place at the subjects home, and both their positive and negative experiences were recorded. Every subject reported some benefit from the MDMA session including positive changes in their attitudes and feelings. Each subject also reported some undesirable physical symptoms and 16 subjects reported undesirable emotional symptoms (anxiety, depression, and insomnia).

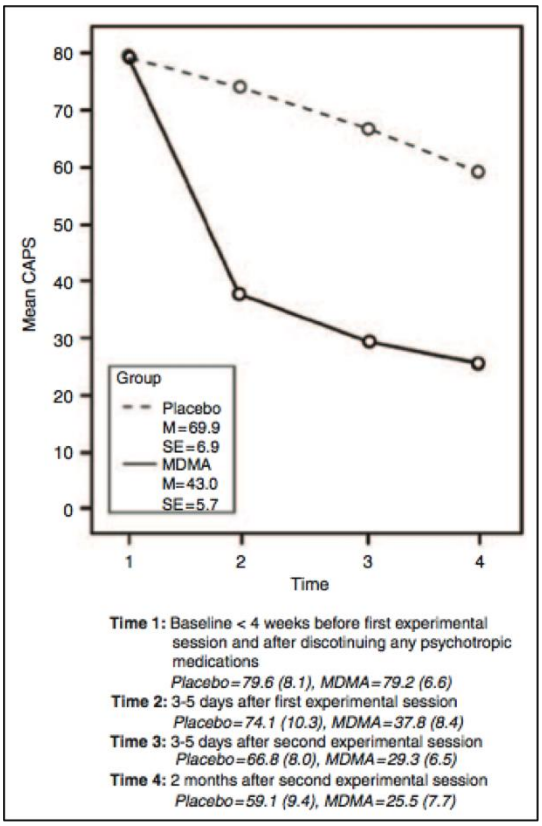
Following its classification as a Schedule I drug, most medical use and testing of the drug ceased, although some therapists continued to use the drug illegally. Most of the work with MDMA in psychotherapy has been performed by MAPS, a non-profit organization dedicated to the development of medical, legal, and cultural contexts for people to benefit from the careful use of psychedelics and marijuana. The group has conducted a number of studies on the use of MDMA in psychotherapy, focusing on its use in patients with PTSD, social anxiety in autistic adults, and anxiety associated with life-threatening illness.

MDMA in PTSD

Greer *et al*. warned against the use of MDMA in psychiatrically vulnerable patients as its use may "predispose people to a recurrence of previous psychological disabilities". Another advocate for MDMA use in psychotherapy also noted that its use should be limited to those patients "who need some assistance in processing difficult emotions that have a deep seated component of fear and/or anxiety" (Doblin, 2002). Those suffering from PTSD fall into this category and it is the reason why this group of patients has been targeted for treatment with MDMA.

Proof of Principle Study

A "proof of principle" randomized, double blind, placebo controlled Phase 2 trial of MDMA in 20 patients with treatment-resistant PTSD was completed in September 2008 (Mithoefer *et al*., 2011). The subjects received two experimental sessions of either psychotherapy with concomitant MDMA administration (n=12) or psychotherapy accompanied by inactive placebo (n=8). The sessions lasted at least seven hours. Subjects were required to meet the DSM-IV criteria for the diagnosis of chronic PTSD and have treatment-resistant symptoms, defined as a CAPS score ≥50, following at least three months of prior serotonin-selective reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) treatment in addition to at least six months of psychotherapy. The primary outcome measure was change in CAPS score two months after the second experimental session. The following graph shows the change in CAPS for MDMA and placebo treated patients over time.



Source: Mithoefer *et al*., 2011

The data show a robust decrease in average CAPS score for the 12 subjects treated with MDMA, compared with a (somewhat surprisingly) small but steady decrease in CAPS score for those administered placebo. Clinical response in this study was defined as a >30% reduction from baseline in CAPS score, which was achieved by 10/12 (83.3%) of the MDMA-treated subjects, compared to 2/8 (25%) in the placebo group. In addition, 10 subjects in the MDMA group no longer met the DSM-IV criteria for PTSD compared with two in the placebo group.

Seven of the eight placebo-treated patients enrolled in an open-label crossover study following completion of the double blind portion of the study. The seven patients treated with MDMA in the crossover study experienced similar decreases in CAPS score as those subjects initially randomized to MDMA treatment, with a mean CAPS score of 65.8 decreasing to 33.9 approximately four to six weeks following the completion of two MDMA psychotherapy sessions.

The most commonly reported side effects that occurred with MDMA treatment were jaw tightness, nausea, feeling cold, dizziness, loss of appetite, and impaired balance. During the week following treatment, irritability and loss of appetite were reported more in those treated with MDMA while insomnia was more common in those treated with placebo. There were no drug-related serious adverse events reported.

A follow up article was published with details on the long-term durability of treatment with MDMA for the 19 subjects that were treated with MDMA psychotherapy (Mithoefer *et al*., 2013). All 19 subjects participated in the long-term follow-up study and 16/19 completed all long-term outcome measures, which were administered an average of 45 months following treatment. The average CAPS score following the completion of the original study (24.6) was not significantly different from the average CAPS score measured on long-term follow up (23.7). Two patients at long-term follow up had CAPS scores >50, which indicates relapse with moderate-to-severe PTSD symptoms. None of the participants in the long-term follow up study felt that there experienced any harm from participating in the original study.

Pilot Study in Veterans and First Responders

A Phase 2 study was conducted with 24 veterans, firefighters, and police offers with service-related PTSD. Subjects were randomized 2:1:1 to receive 125 mg of MDMA, 75 mg of MDMA, or placebo combined with three experimental day-long psychotherapy sessions approximately three to five weeks apart. All subjects also received weekly non-drug psychotherapy. The study concluded in October 2016, and according to the MAPS website the data are being prepared for analysis and publication in a peer-reviewed scientific journal.

Phase 3 Clinical Plan

On November 29, 2016, the U.S. Food and Drug Administration approved the protocol for two Phase 3 clinical trials of MDMA in PTSD. These studies are scheduled to commence in June 2017. Since MAPS is a non-profit organization, a fundraising drive is currently underway to be able to procure enough MDMA produced under current Good Manufacturing Practices (cGMP) to conduct the Phase 3 studies. The trial protocol will be similar to the pilot study in veterans described above, however the number of patients in each of the two trials will likely be at least 230.

Potential Issues With MDMA Treatment

While the data described above are certainly encouraging, and the news of MDMA use in treating PTSD has highlighted the significant problem of few treatment options available for those suffering from PTSD, there are a number of issues with MDMA treatment that could preclude its approval and/or widespread use.

1) MDMA is currently illegal in the U.S. If an exception were to be made for its use with psychotherapy for the treatment of PTSD, it may lead to the belief that the drug is safe for repeated personal use or for conditions for which it may not be effective as some patients attempt to "self medicate". While the use of MDMA for three times as part of the protocol for treating PTSD is unlikely to lead to any permanent negative effects, repeated use of MDMA can lead to increased psychiatric symptoms (MacInnes *et al*., 2001).
2) There are known neurotoxicity issues with repeated use of MDMA (Kish *et al*., 2010). While the argument could be made that the protocol set forth by Mithoefer *et al*. limits an individuals exposure to MDMA, how the FDA would ultimately handle the approval of a potentially neurotoxic drug is a large unknown at this point.
3) It is difficult to discern if MDMA is responsible for the effects seen in the clinical trials due to the difficulty with truly blinding both participants and therapists. In the study from Mithoefer *et al*., 19/20 subjects correctly guessed their drug condition, while all of the therapists did so. Thus, at least for that study, the case could be made that the results seen could be due at least in part to the unintentional unblinding of the participants.
4) The MDMA psychotherapy sessions last all day and are part of a much larger number of psychotherapy sessions. It is unclear how this treatment could be applied to a diagnosed PTSD population of approximately 600,000 U.S. veterans (and a potential total PTSD population of greater than 8 million in the U.S.) as there are not likely to be sufficient resources to treat appreciable numbers of patients with the protocol described by Mithoefer *et al*.

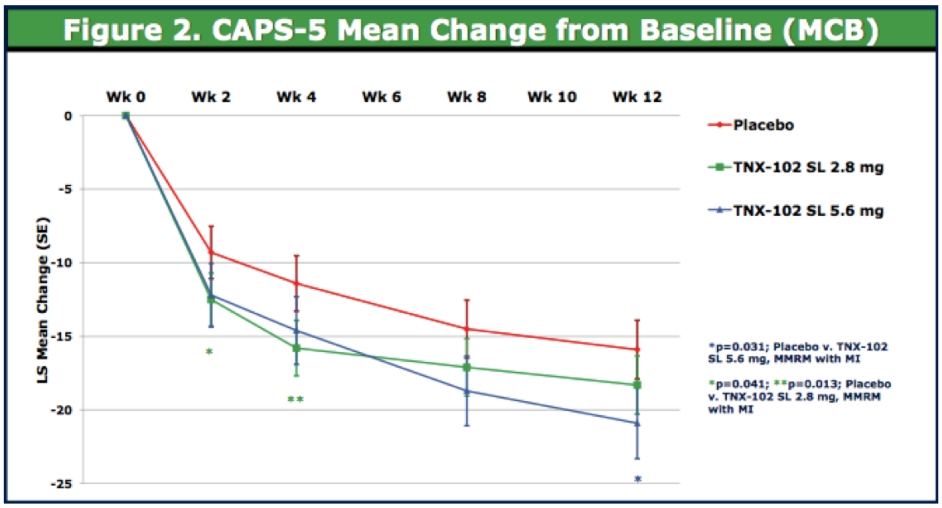
Tonix Phase 3 Program in PTSD Set to Get Underway in 1Q17

Tonix's lead product, TNX-102 SL, is currently being developed for the treatment of PTSD. TNX-102 SL is a small, rapidly disintegrating tablet of cyclobenzaprine (CBP) for sublingual administration and transmucosal absorption. CBP is the active ingredient of two products that are FDA approved in the U.S. for the treatment of muscle spasms.

These products are sold as immediate-release tablets and extended-release capsules. The sublingual formulation has a differentiated pharmacokinetic profile from the oral immediate-release CBP tablet as exemplified by a 154% higher bioavailability, 338% higher plasma levels during the first hour after dosage, and substantially lower production of norcyclobenzaprine due to the decrease in first-pass hepatic metabolism.

In May 2016, Tonix announced positive results from the AtEase Phase 2 clinical trial of TNX-102 SL in patients with military-related PTSD. The three-arm trial enrolled 231 participants, who were randomized to receive either 2.8 mg of TNX-102 SL (n=90), 5.6 mg of TNX-102 SL (n=49), or placebo (n=92) taken sublingually at bedtime daily for 12 weeks. The primary endpoint of the trial was the week 12 mean change from baseline in the total CAPS-5 score, which is shown in the following graph. Unfortunately, a direct comparison with the results from the study by Mithoefer *et al*. is not possible as that study utilized the CAPS-IV score while the study performed by Tonix utilized the updated CAPS-5 score.

Figure 2. CAPS-5 Mean Change from Baseline (MCB)



Source: Sullivan *et al*., 2016

On December 8, 2016, the company presented additional data from the Phase 2 study showing the potential for TNX-102 SL to treat combat-related PTSD patients, who are typically the most difficult to treat. Combat-related PTSD represented the majority of index traumas in the Phase 2 study (85%, n=197). This sub-group was analyzed according to baseline CAPS-5 score of either ≥ 33 or the whole population with a baseline CAPS-5 score of ≥ 29. The following table shows a significantly greater improvement in CAPS-5 total score, CAPS-5 clusters in intrusion (Cluster B) and hyperarousal (Cluster E), and in certain measures (e.g., sleep quality) in the 5.6 mg TNX-102 SL group.

Table 4. Week 12 Outcome Measures for TNX-102 SL 5.6 mg v. Placebo in Combat-Only PTSD for Both Entry Thresholds

	PBO N=74, 5.6mg N=46; CAPS-5 ≥ 29		PBO N= 64, 5.6mg N=35; CAPS-5 ≥ 33	
Outcome Measure	ES[1]	p-value[2]	ES[1]	p-value[2]
CAPS-5				
Total score	0.42	*0.037	0.57	*0.013
Cluster B (intrusion)	0.26	0.183	0.50	*0.031
Cluster C (avoidance)	0.04	0.824	0.11	0.570
Cluster D (mood/cognition)	0.41	*0.035	0.42	0.061
Cluster E (arousal and reactivity)	0.40	*0.036	0.57	*0.012
E6 (Sleep item)	0.58	*0.003	0.58	*0.010
E2 (Reckless/Self Destruct)	0.15	0.178	0.30	*0.019
CGI–I (responders)	2.15	*0.049	2.12	0.082
SDS				
Total Score	0.41	*0.039	0.47	*0.032
Work/School item	0.40	*0.026	0.40	*0.015
Social/Leisure item	0.50	*0.013	0.51	*0.028
Family Life/Home Responsibilities item	0.19	0.328	0.22	0.274

Source: Sullivan *et al*., 2016

Phase 3 Development Plan

Tonix is currently developing a Phase 3 program for the 5.6 mg dose of TNX-102 SL in PTSD. Following a successful end-of-Phase 2 meeting with the FDA, the company announced that the meeting minutes indicated that positive results from two adequate, well-controlled Phase 3 efficacy and safety studies and long-term (six- and 12-month) safety exposure studies would support the registration of 5.6 mg TNX-102 SL for the treatment of PTSD. Importantly, the same primary endpoint that was used in the Phase 2 study will be used for both upcoming Phase 3 studies. Importantly, the company has already produced all of the TNX-102 SL for the Phase 3 studies.

The first Phase 3 clinical trial will be in military-related PTSD and be similar to the recently completed Phase 2 study. The trial is likely to begin in the first quarter of 2017 and we anticipate enrollment of approximately 550 patients divided evenly between placebo and 5.6 mg TNX-102 SL treatment. We expect topline data to be available in the fourth quarter of 2018. The company will be performing up to two planned interim analyses to test for efficacy or sample size adjustment: the first will be conducted when approximately 30% (~180 patients) of the total planned enrollment is evaluable for efficacy and the second analysis after 50% (~270 patients) of the total planned enrollment is eligible for efficacy. The study will be limited to those patients with a CAPS-5 score ≥33 (indicating moderate to severe PTSD). The primary endpoint will be the mean change from baseline in total CAPS-5 at Week 12 between those treated with TNX-102 SL 5.6 mg and placebo.

The second Phase 3 study will involve individuals with any type of PTSD. The reason for this is because the company will need to show efficacy in a broad population of patients with PTSD in order for a label of treating PTSD, not just military-related PTSD. In addition, since the military-related PTSD studies have predominantly male subjects, the FDA will require data in a larger female PTSD population. The second Phase 3 study will also be limited to those with a CAPS-5 score ≥33 and will likely enroll approximately 550 patients. The primary endpoint will be the mean change from baseline in total CAPS-5 at Week 12 between those treated with TNX-102 SL 5.6 mg and placebo.

Conclusion

MDMA can now be considered another “Phase 3 ready” asset for the treatment of PTSD, however we note that Tonix is ahead in development simply due to the fact that all Phase 3 material has been produced, while the investigators for the MDMA Phase 3 program are continuing to raise money to be able to produce enough MDMA for the Phase 3 clinical trials. Whether this will occur in time to initiate the Phase 3 program in June 2017, which MAPS is currently guiding for, is unknown.

We are glad to see the extra media attention for those suffering from PTSD brought about by MDMA, as we feel the general public has a very limited understanding of the plight these patients face. The fact that patients are willing to try a psychedelic drug for treating their PTSD speaks to the fact that so few treatment options are currently available for this debilitating condition.

It is quite difficult to directly compare the efficacy of MDMA psychotherapy sessions with TNX-102 SL treatment, but we feel that TNX-102 SL has a number of advantages over MDMA, including the fact that TNX-102 SL is not a psychedelic drug, there have been no reports linking cyclobenzaprine to neurotoxicity, and TNX-102 SL treatment will be able to continue for an extended time period, while MDMA treatment would be limited to three doses, with each taken prior to a psychotherapy session.

We will continue to follow the development of MDMA treatment in PTSD and will provide an update when the results from the pilot study in veterans are published. For now, we continue to believe that Tonix is the leading developer of a potential PTSD pharmacotherapy treatment. In addition, we don’t believe that MDMA would take a significant portion of market share were it to be approved and would likely be reserved for severe PTSD cases, thus our valuation for Tonix is not changed and remains $2.00 per share.

PROJECTED FINANCIALS

Tonix Pharmaceuticals Holding Corp.
Income Statement

Tonix Pharmaceuticals	2015 A	Q1 A	Q2 A	Q3 A	Q4 E	2016 E	2017 E	2018 E
TNX-102 SL (FM)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
TNX-102 SL (PTSD)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Research & Collaborations	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
CoGS	$0	$0	$0	$0	$0	$0.0	$0.0	$0.0
Product Gross Margin	-	-	-	-	-	-	-	-
R&D	$35.5	$10.7	$7.5	$5.5	$5.0	$28.7	$17.0	$20.0
SG&A	$12.7	$3.3	$2.3	$2.1	$2.2	$10.0	$8.0	$8.5
Operating Income	($48.2)	($14.0)	($9.8)	($7.6)	($7.2)	($38.7)	($25.0)	($28.5)
Operating Margin	-	-	-	-	-	-	-	-
Interest & Other Income	$0.1	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($48.1)	($14.0)	($9.8)	($7.6)	($7.2)	($38.7)	($25.0)	($28.5)
Taxes & Other	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($48.1)	($14.0)	($9.8)	($7.6)	($7.2)	($38.7)	($25.0)	($28.5)
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($2.86)**	**($0.74)**	**($0.50)**	**($0.29)**	**($0.19)**	**($1.52)**	**($0.56)**	**($0.57)**
YOY Growth	*3.5%*	-	-	-	-	*-46.9%*	*-63.5%*	*2.6%*
Weighted Shares Outstanding	16.8	18.9	19.7	26.1	37.0	25.4	45.0	50.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

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