RESEARCH REPORT ON
POST TRAUMATIC STRESS DISORDER
(PTSD)

Revision History

Rev.	Description	Date	Authors
1.0	Final version	30-JUN-2022	ReST THERAPEUTICS Aline Freyssin Aude Michaud Florent Perin-Dureau Gilles Rubinstenn
2.0	Annual report updates of the following sections: • §2.2.1 Clinical trials on PTSD - all types of interventions combined (ongoing clinical trials) • §1.4 Ongoing clinical trials on PTSD • §2 PTSD industrial players in clinical phase • §4.2 Molecules repositioned from an indication other than PTSD • §4.3 New molecules • §5 Biomarkers under PTSD • Conclusion	13-FEB-2023	ReST THERAPEUTICS Aline Freyssin Aude Michaud Florent Perin-Dureau Gilles Rubinstenn

Table of contents

Table of illustrations

Introduction

Psychological traumas have been reported in soldiers since Antiquity. Interest in them then developed through military medicine in the 17th century. But it is the violence of the great international conflicts of the 20th century that will impose the deepening of knowledge on psycho-traumatic disorders. At the same time, the description and study of similar disorders in civil society have been reported in the scientific literature as early as the 19th century. Nevertheless, the concept of post-traumatic stress disorder, as we know today, was not clinically defined until 1980, following the ravages of the Vietnam war among American veterans.

Post-Traumatic Stress Disorder (PTSD) is a psychiatric disorder affecting the life of people who have experienced a psychologically traumatic or witnessed event. Such event can be a natural disaster, a serious accident, a terrorist act, war/combat, or rape or who have been threatened with death, sexual violence or serious injury.

The PTSD international diagnostic reference is the "Diagnostic and Statistical Manual of Mental Disorders" (DSM), based on scientific literature with contributions from more than 200 subject matter experts. Currently the most frequently used version is DSM-5. The following symptoms are simultaneously identified: at least one intrusion symptom (traumatic event re-experiencing such as nightmares, …), one avoidance symptom (avoidance of trauma-related stimuli such as trauma-related thoughts, …), two arousal and reactivity symptoms (negative affect, decreased interest in activities, …), and two cognition and mood symptoms (irritability, risky or destructive behavior, …).

PTSD is sometime difficult to identify and assess because individual PTSD symptoms are found in other mental illnesses such as sleeping disturbance, substance(s) abuse, feeling isolated or even overly negative thoughts and assumptions about oneself or the world.

Among adults who experience a traumatic event, not everyone will develop PTSD. Acute PTSD occurs when duration of symptoms is between one and three months after the traumatic event and chronic PTSD occurred if symptoms last longer than 3 months. In severe forms, long lasting PTSD can affect the life of patient for several years. A common consensus exists along the fact that a patient whose PTSD does not disappear within 12 months will develop long lasting disorder.

PTSD is a public health problem; it affects about 15.4 million adults evenly distributed between Europe and U.S. In a recent survey the total annual economic burden for US society for PTSD reaches to $232 billion, including $76.1 billion in medical cost and $46.2 billion in unemployment for the civil population. The part of the economic burden concerning veterans reaches $42.7 billion.

The objective of this report* is to draw a mapping on scientific and business data on the management of PTSD in term of clinical studies, industrial players in clinical phase, existing molecules and new molecules, intellectual properties, and biomarkers. Thus, this report provides a scientific and business support for the establishment of the clinical and business strategies of the new FENM (FluoroEthylNorMemantine) molecule developed by ReST Therapeutics in the prevention and treatment of PTSD.

*** The Clinical Trials database was used to collect all the clinical trial data in this report. Searches were conducted on February 2, 2022, for the general parts and on February 6, 2023, for updating ongoing clinical trials for this V2 report version.***

1. Clinical trials of PTSD

As the development cycle of a molecule is on average 7 years, the research results were presented in two groups (clinical trials initiated before 2015/clinical trials initiated after 2015) in order to be able to distinguish between molecules studied more than one development cycle earlier (*whether or not they have led to market authorization in the management of PTSD)* and currently investigated molecules *(so still having the possibility of obtaining a market authorization, regardless of the outcome of an individual study*).

First and foremost, research has been carried out to determine whether the trials recorded on PTSD in the Clinical Trials database follow the trend of recording all trials in psychiatry as well as trials of all indications.
As a word of caution, sponsors do not systematically inform their trials in this database, even if registration in the database has been increasingly carried out in recent years. Also, this database being American, the US clinical trials are more informed than those of other countries. Nevertheless, Clinical Trials is today the most complete database worldwide.

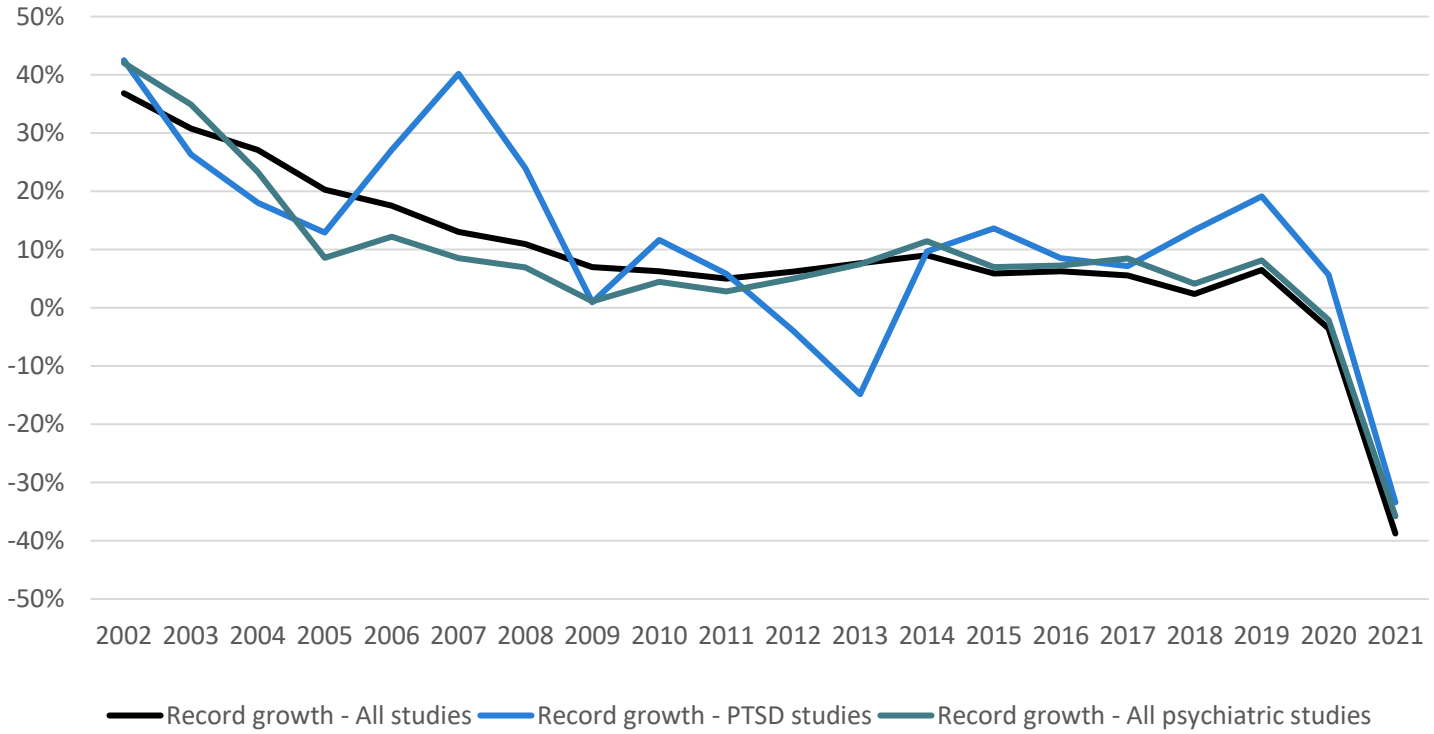


Figure1: Monitoring the evolution of the number of clinical trials registered in the database ClinicalTrials.gov

Figure 1 shows that overall, the number of clinical trials registered with PTSD follows the trend in the number of clinical trials registered in psychiatry as well as the number of registered clinical trials for all conditions. Fewer clinical trials have been registered in 2021, probably in connection with the Covid 19 outbreak.

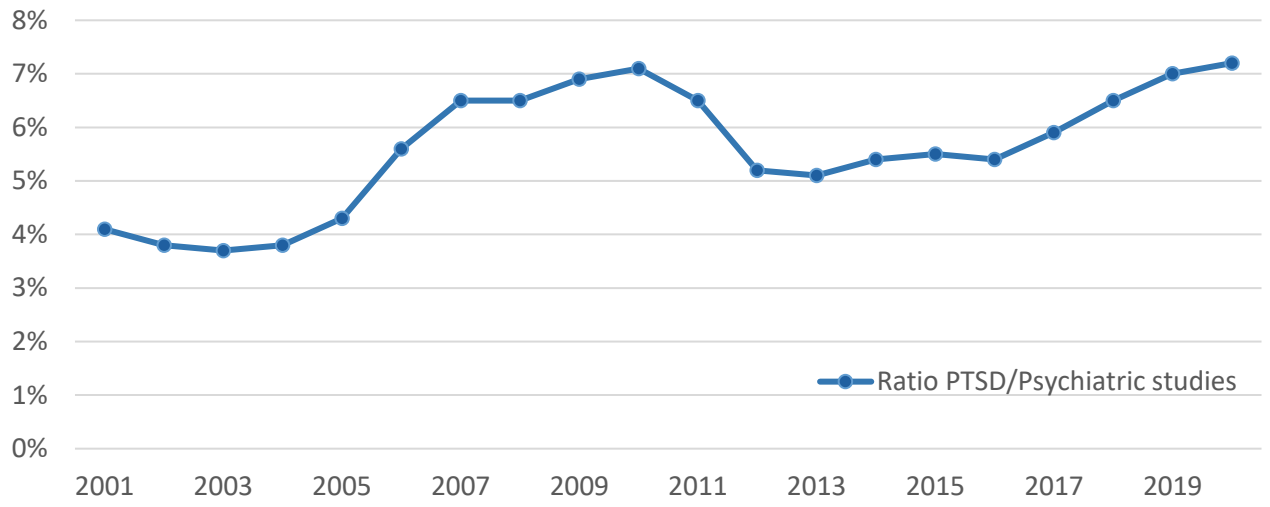


Figure2: Monitoring the evolution of the PTSD/Psychiatry clinical trials ratio

Figure 2 shows the trend on PTSD centered clinical trial, compared to all trials conducted in psychiatry. Although the percentage is fluctuating a clear growing trend exists PTSD trials accounted for 4% of psychiatric trials in 2001 and 7% of psychiatric trials in 2020. This trend is noteworthy as even if PTSD is a severe affection, it does not account for 7% of psychiatric diseases. This clear excess in interest in PTSD by the clinical community can be interpreted as an increased search of an efficient treatment.

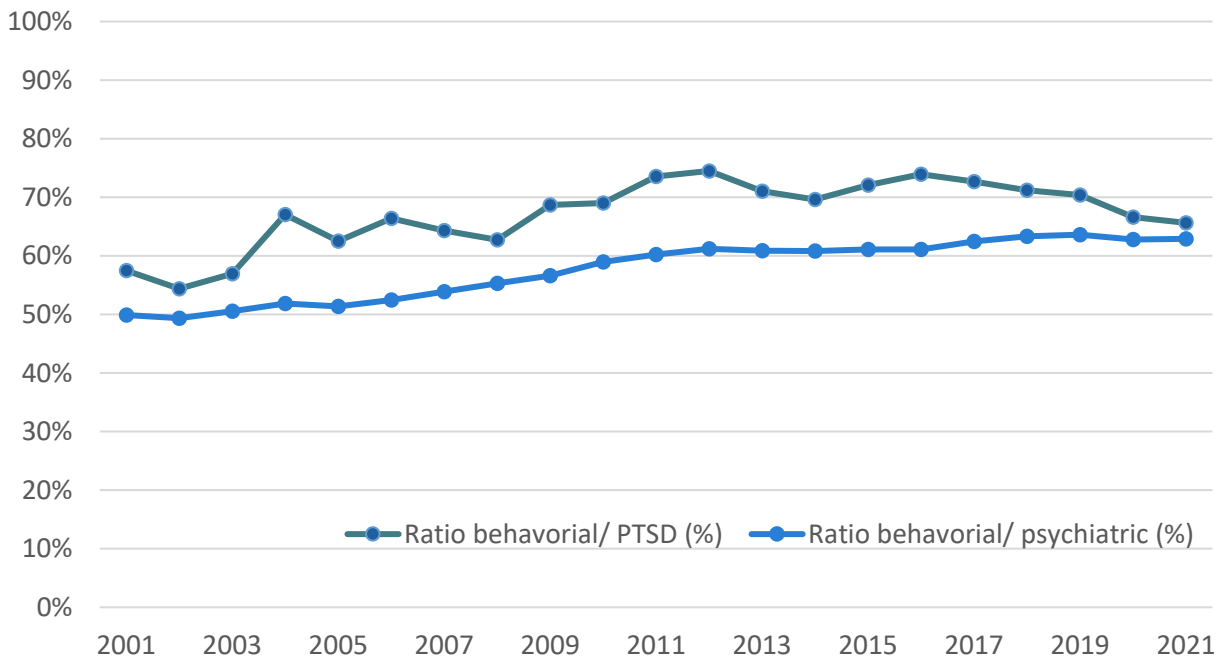


Figure3: Monitoring the evolution of the ratios of psychotherapy/PTSD clinical trials to psychotherapy/psychiatry clinical trials

Figure 3 shows that clinical trials on PTSD are more often conducted in combination with psychotherapy than all clinical trials conducted in psychiatry. Nevertheless, in recent years, trials on PTSD with a psychological therapy component have been declining, approaching the number of trials conducted in psychiatry with a psychotherapy component (around 65% in 2021).

Start date	End date	Total trials registered	Record growth	PTSD trials (Including psychotherapy)	Record growth (Including psychotherapy)	Psychiatric disorder trials (Including psychotherapy)	Record growth (Including psychotherapy)
01/01/ 2001	31/12/ 2005	48 191	–	179 (49 (27%))	–	3724 (1914 (51%))	–
01/01/ 2006	31/12/ 2010	102 434	53%	476 (256 (54%))	166% (+27%)	6883 (3767 (55%))	85% (+4%)
01/01/ 2011	31/12/ 2015	145 236	29%	625 (392 (63%))	31% (+9%)	8926 (5444 (61%))	30% (+6%)
01/01/ 2016	31/12/ 2020	186 583	22%	887 (533 (60%))	42% (-3%)	12800 (8020 (63%))	43% (+2%)

Table 1: Monitoring of the progress of the tests recorded in the ClinicalTrials.gov database

As a final check we analyzed the report of clinical trial registration for both PTSD and Psychiatry in table 1. There was greater growth in the registration of clinical trials in the ClinicalTrials.gov database during the period 2006-2010, whether for trials conducted on PTSD, psychiatric disorders or all trials registered in the database. The evolution of the recording of trials in the database follows the same trend in all three cases, meaning that the data in this database are rather representative of all the trials conducted.

1.1. Breakdown of clinical trials by type of intervention

Prior to 2015**, 833 clinical trials** on PTSD were registered.

	Avant 2000	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
Behavioral	10	3	4	8	3	12	16	20	18	42	38	37	45	67	50	39	412
Device	1					1			1	4	1	4	3	5	5	6	31
Drug	4		6	9	13	11	13	11	10	19	20	22	12	21	17	14	**202**
Other	6	3	3	3	5	5	6	6	7	21	19	22	26	22	17	17	188
Grand Total	**21**	**6**	**13**	**20**	**21**	**29**	**35**	**37**	**36**	**86**	**78**	**85**	**86**	**115**	**89**	**76**	**833**

Table 2: Classification by type of intervention and year of clinical trials on PTSD (before 2015)

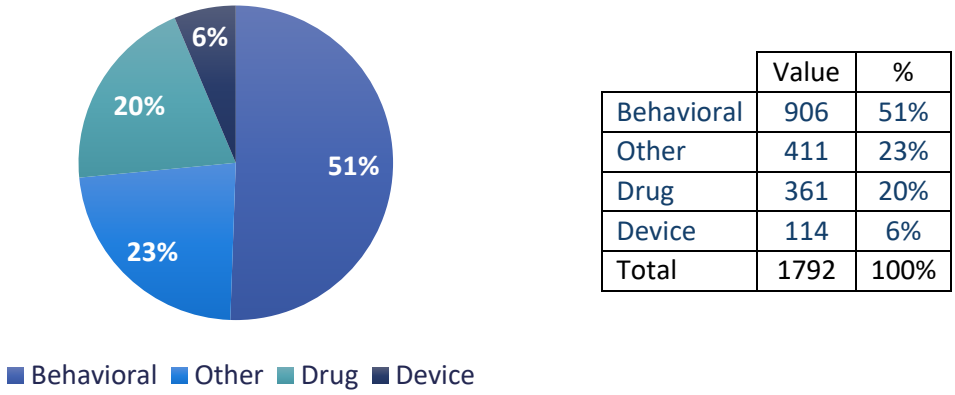
During the period 2015-2022, **959** clinical trials on PTSD have been registered, an absolute increase of **164%.**

	2015	2016	2017	2018	2019	2020	2021	2022	Total
Behavioral	46	60	56	57	76	82	78	39	**494**
Device	11	8	6	10	18	13	11	6	**83**
Drug	15	22	20	13	20	14	38	17	**159**
Other	16	24	19	28	34	42	50	10	**223**
Grand Total	**88**	**114**	**101**	**108**	**148**	**151**	**177**	**72**	**959**

Table 3: Classification by type of intervention and year of clinical trials on PTSD (period 2015-2022)

In the rest of the report, data showing interesting differences between periods before 2015/ 2015-2022 are presented; otherwise, only pooled data from these two periods will be presented.

A total of **1792 clinical trials** were recorded on PTSD at the beginning of 2022 year, with the following breakdown by type of intervention:



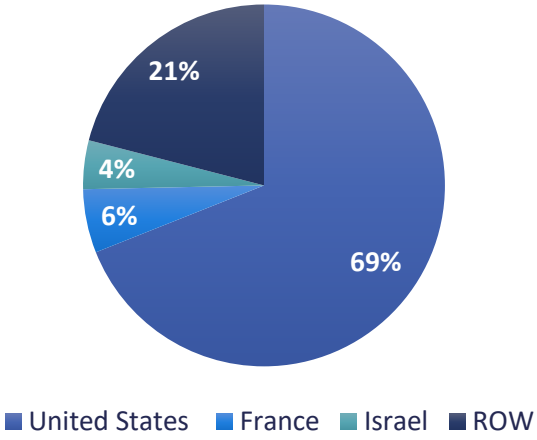
	Value	%
Behavioral	906	51%
Other	411	23%
Drug	361	20%
Device	114	6%
Total	1792	100%

Figure 4: Classification by type of intervention of the 1792 clinical trials registered on PTSD.

"Behavorial" trials account for half of clinical trials on PTSD while 1 in 5 trials is conducted on a molecule.

1.2. Geographical distribution of clinical trials on PTSD

1.2.1. Clinical trials on PTSD - all types of interventions combined

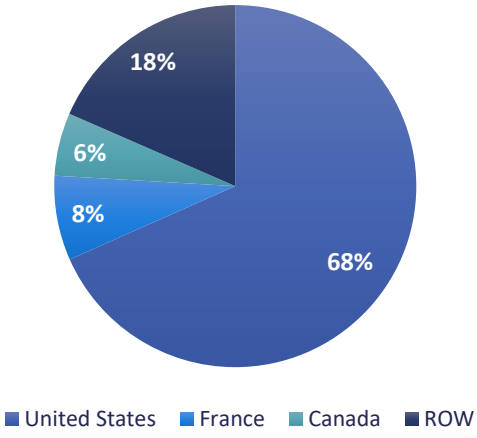


	Value	%
United States	1236	69%
France	102	6%
Israel	78	4%
ROW	376	21%
Total	1792	100%

Figure5: Geographical distribution of the 1792 registered clinical trials on PTSD

Nearly 70% of clinical trials conducted on PTSD are conducted in the United States. The France is the second country with the highest number of clinical trials of PTSD, followed by Israel.

This geographical distribution is compared with that of ongoing clinical trials:



	Value	%
United States	389	68%
France	43	8%
Canada	32	6%
ROW	105	18%
Total	569	100%

Figure 6: Geographic distribution of the 569 ongoing clinical trials on PTSD

The geographical distribution of ongoing clinical trials of PTSD is comparable to all trials recorded over all time periods. However, Canada ranks third among countries with the highest number of ongoing clinical trials. These data are similar to those of last year.

Geographical distribution according to the population studied (veterans/civilian population):

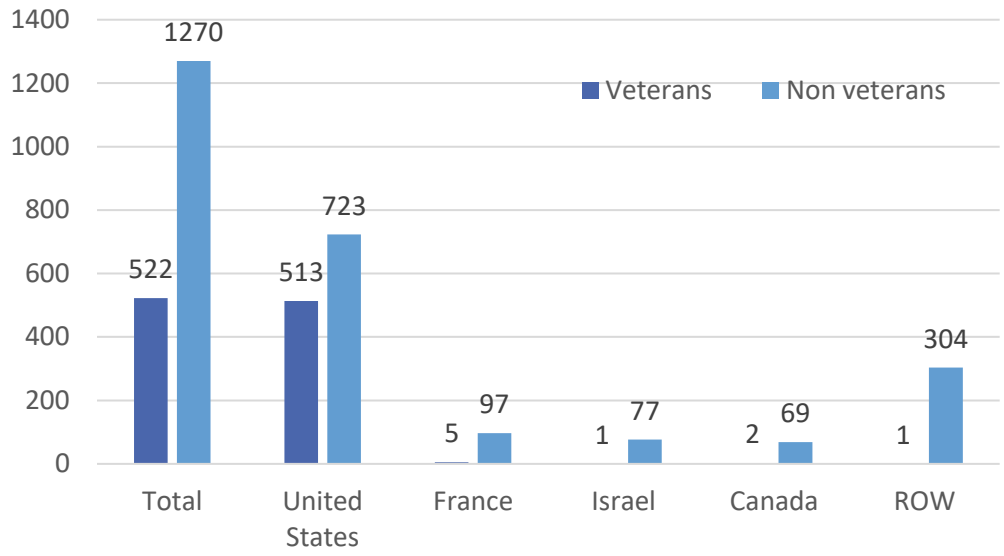


Figure7: Geographical distribution of the 1792 registered clinical trials on PTSD

The majority (71%) of PTSD clinical trials are conducted in the civilian population. 98% of the clinical trials conducted on the military population are conducted in the United States.

1.2.2. Clinical trials on PTSD conducted on a medical device

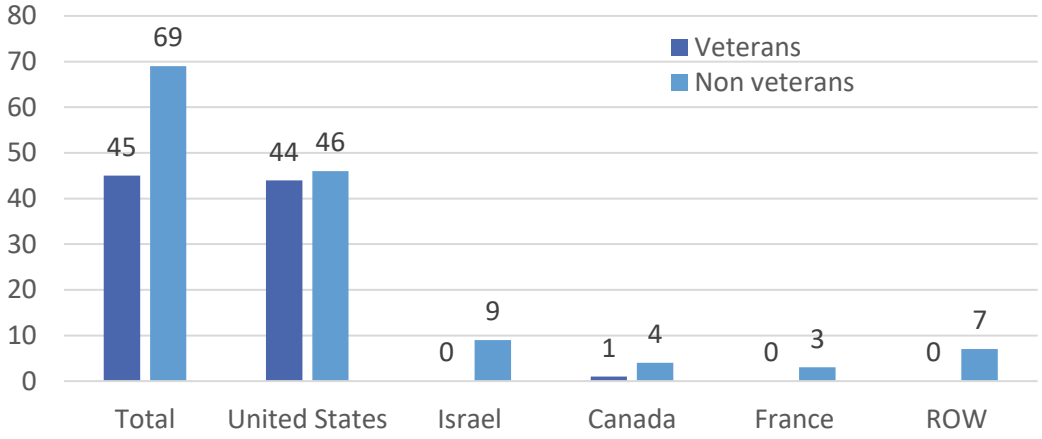


Figure8: Location of the 114 registered device clinical trials

The majority (60%) of clinical trials involving a medical device are conducted in the civilian population. 98% of trials conducted on the military population when a medical device is studied are conducted in the United States.

1.2.3. Clinical trials on PTSD conducted on behavioral therapy

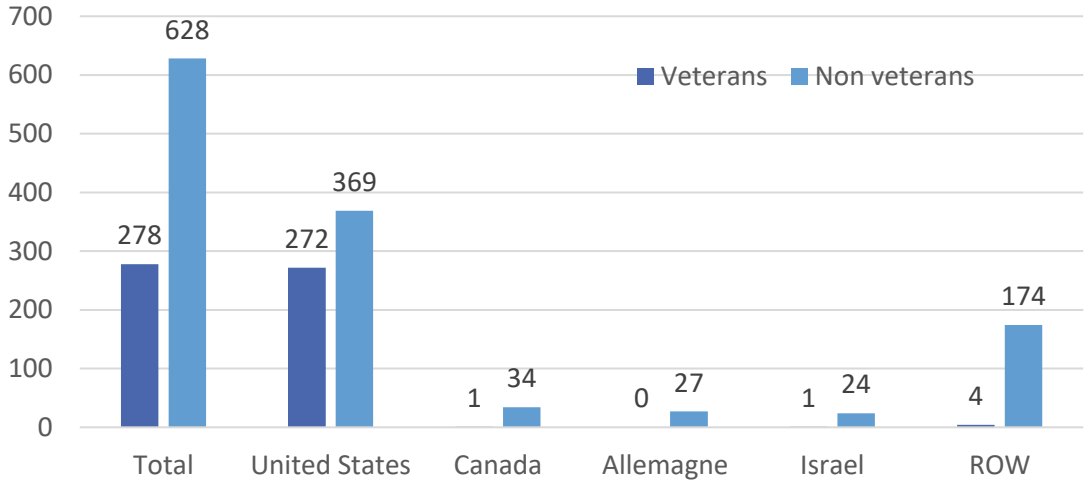


Figure9: Location of the 906 "behavorial" clinical trials

The majority (69%) of behavioral clinical trials are conducted in the civilian population. 98% of trials conducted on the military population when behavioral therapy is studied are conducted in the United States.

1.2.4. Clinical trials on PTSD conducted on a molecule

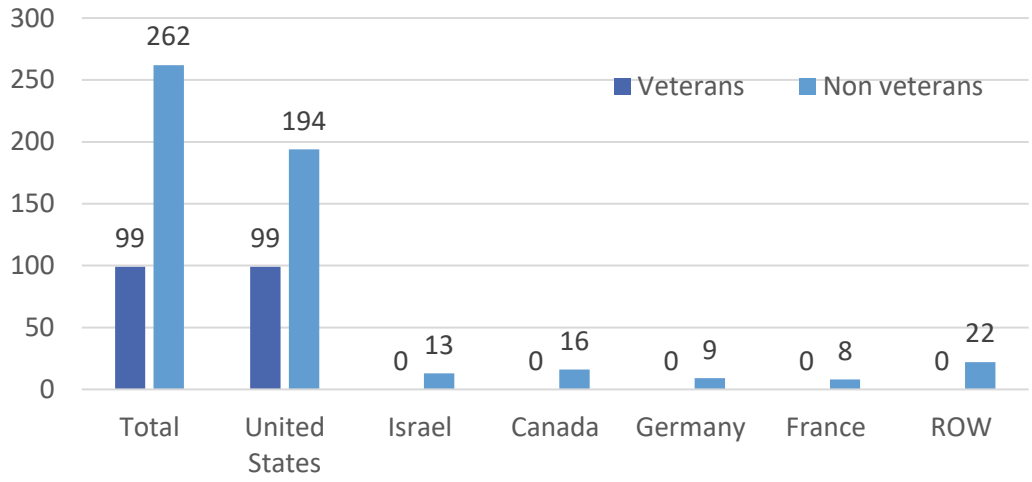


Figure10: Location of the 361 registered drug clinical trials

The majority (76%) of clinical trials involving a molecule are conducted in the civilian population.
All trials conducted on the military population when a molecule is studied are conducted in the United States.

1.2.5. General conclusion for PTSD Clinical Trials breakdown

Overall:

- United States is a major place for PTSD (69%), regardless of the type of intervention (molecule, behavioral therapy, medical device, other)

- Outside the United States, France, Israel and Canada are the 3 countries in which the most tests are recorded

- France is the country where the number of trials has increased the most over time, from 3% (24) before 2015 to 8% (78) over the current period, becoming the second most represented region

- They are mainly (71%) carried out on the civilian population

- The majority of trials on veterans (98%) are carried out by the United States

- An ever-increasing number of geographical regions involved over the years

Currently:

- 67% of registered clinical trials are in the United States

- 73% are recorded in Nord America (6% in Canada)

- France is the second country with the most tests (9%)

- France accounts for half of the trials conducted in Europe (6% and 5% in various Eastern and Northern European countries, respectively)

1.3. Clinical trials conducted on molecules in PTSD detailed by phase and by period

121 molecules were registered on PTSD in **359 clinical trials**, including 155 clinical trials over the period 2015-2022 and 204 trials before 2015 (details in Annex 3).

66 molecules are considered to **potentially have an action on PTSD,** including:

- The **9 molecules that have been subject of the largest number of clinical trials.** They are all known. Two of them (in blue) have obtained a Market Authorization for PTSD management:
  - Propranolol (24 trials)
  - MDMA (22 trials)
  - Ketamine (21 trials)
  - Prazosin (19 trials)
  - Paroxetine (14 trials)
  - Oxytocin (14 trials)
  - Sertraline (13 trials)
  - Hydrocortisone (11 trials)
  - Topiramate (10 trials)
- **12 new molecules**:
  - ALTO-100
  - BI 1358894
  - BNC210
  - CORT108297
  - JPZ150
  - Lu AG06466
  - NBTX-001
  - NYX-783
  - PT-150
  - SRX246
  - TNX - 102 SL
  - TTI-0102
- **45 other molecules**
  - Aleozen
  - Brexanolone
  - Brexpiprazole
  - Buprenorphine
  - Buprenex
  - CBD
  - Clonidine
  - Dexamethasone
  - Dexmedetomidine
  - DHEA
  - Doxazosin
  - Dronabinol
  - Escitalopram
  - Estradiol
  - Eszopiclone
  - Fluoxetine
  - Insulin
  - L-DOPA

- Lipopolysaccharide
- Lofexidine
- Losartan
- Methylphenidate
- Mianserin
- Minocycline
- N-Acetylcysteine
- Neuropeptide Y
- Nitrous Oxide
- Pimavanserin
- Pregabalin
- Pregnenolone
- Progesterone
- Psilocybin
- Quetiapine
- Ramelteon
- Riluzole
- Ropivacaine
- Serotonin
- Suvorexant
- THC
- THC et CBD
- Trazodone
- Venlafaxine
- Vortioxetine
- Zonisamide

55 molecules are considered **abandoned** (highlighted in green in the table in Appendix 3) due to no clinical study registration since 2015, including:

- **8 new molecules**
  - Lanicémine AZD6765
  - GSK561679 (Verucerfont)
  - Orvepitant
  - PF-04457845
  - Pomaglumetad Methionil
  - PRX-03140
  - SNC-102
  - SYN117 (Nepicastat)
- **47 other molecules**
  - Aprepitant
  - Aripiprazole
  - Asenapine
  - Atomoxetine
  - Atorvastatin
  - Bupropion
  - Carvedilol
  - Cortisol
  - D-Cycloserine
  - Desvenlafaxine
  - Diazepam
  - Divalproex
  - D-Serine
  - Dobutamine
  - Duloxetine
  - Enbrel
  - Fluticasone propionate 2
  - Ganaxolone
  - Guanfacine
  - Haloperidol
  - Ifenprodil
  - Iloperidone
  - Keto Dehydroepiandrosterone
  - Levetiracetam
  - Lithium Carbonate
  - Memantine
  - Methylene Blue
  - Mifepristone
  - Mirtazapine
  - Modafinil
  - Nicotine
  - Omega-3
  - Oxygen
  - Paliperidone
  - Phenytoin
  - Pramipexole
  - Prednisone
  - Rapamycin
  - Risperidone
  - Seromycin
  - Syntocinon
  - Tramadol
  - Varenicline
  - Vilazodone
  - Xyrem
  - Yohimbine
  - Ziprasidone

4 Biomarkers

- [18F] SPA-RQ
- [11C] MENET
- [11C] MK-3168
- [18F]-FDG (Fluorodeoxyglucose)

121 molecules were registered on PTSD in 359 clinical trials, 12 new molecules are to be considered and 54 molecules with market authorization in an indication other than PTSD should be considered in the management of PTSD.

1.4. Ongoing clinical trials on PTSD

1.4.1. Sponsors of ongoing clinical trials

Searches on the Clinical Trials database were conducted on February 6, 2023, for updating this section.

94% (533) of clinical trials are **academic and 6%** (35) have an **industrial** sponsor, the breakdown is exactly the same than last year (2023 vs 2022). Thirty more trials are registered compared to last year (568 vs 539).

Sponsor	Number of clinical trials	%
Academic	533	94
Industrial	35	6
Total	**568**	**100**

Below are listed the **industrial sponsors,** currently having at least one clinical trial in progress **on "drug"** and PTSD (24 trials):

In green: ongoing clinical trials last year and always registered ongoing.
In grey: ongoing clinical trials last year and now closed.
Without color: new ongoing clinical trials this year.

Industrial sponsor name	Drug	Country	Phase	NCT number
Otsuka Pharmaceutical	Brexpiprazole + Sertraline	USA	3	NCT04124614
	Brexpiprazole + Sertraline	USA	3	NCT04174170
	Propranolol or Prazosin + Brexpiprazole + Sertraline	USA	1	NCT05189977
Jazz Pharmaceuticals	JZP150	USA	2	NCT05178316
	Cannabinoids (THC and CBD) Withdrawn study (evaluation of pandemic-related challenges impacting both clinical trial sites and potential participants. This suspension was initiated prior to site activation and participant recruitment)	Ireland	2	NCT04592159
H. Lundbeck A/S	Lu AG06466	USA	1	NCT04597450
Bionomics Limited	BNC210	USA/UK	2	NCT04951076
Boehringer Ingelheim	BI 1358894	USA	2	NCT05103657
Alto Neuroscience	ALTO-100 Completed study (2 new ongoing studies on MDD)	USA	2	NCT05117632
Aptinyx	NYX-783	USA	2	NCT05181995
Nobilis Therapeutics Inc.	NBTX-001	USA	2	NCT03635827
COMPASS Pathways	Psilocybin	UK	2	NCT05312151
Halucenex Life Sciences Inc.	Psilocybin	Canada	2	NCT05243329
TruDiagnostic (collab. Wild Health)	Ketamine	USA	2	NCT05294835
Ananda Scientific Inc.	Cannabidiol (CBD)	USA	2	NCT05269459
Bionorica SE	BX-1 (dronabinol)	Germany	2	NCT04448808
Sage Therapeutics	Brexanolone (IV) (Zulzesso)	USA	4	NCT05254405
	Brexanolone	USA	1	NCT05223829
BioXcel Therapeutics Inc	Dexmedetomidine sublingual (BXCL501)	USA	1	NCT04827056
Pfizer	Dexmedetomidine vs Midazolam	USA	3	NCT04801589
ACADIA Pharmaceuticals Inc.	Pimavanserin	USA	4	NCT04809116
	Pimavanserin	USA	2	NCT05441280
Tonix Pharmaceuticals, Inc.	TNX-102 SL	Kenya	2	NCT05372887
Hoffmann-La Roche	Balovaptan	USA	2	NCT05401565
MAPS Europe B.V.	MDMA	EU & UK	2	NCT04030169

OMNI Medical Services, LLC	Cannabis, medical	USA	2	NCT03944447

Table 4: Listing of ongoing industrial clinical trials on drugs and PTSD

Manufacturers with one or more ongoing clinical trials on a molecule are presented in part (2) of the report (except Bionorica SE which is focused on treatment with plants and WILD 5 Wellness which is focused on wellness development programs).

Below are listed the **industrial sponsors,** currently having at least one clinical trial in progress **on "device"** and PTSD (8 trials):

Industrial sponsor name	Device	Country	NCT number
Neurovalens Ltd	Modius Sleep (vestibular nerve stimulation) Withdrawn study (new trial opportunity in the USA)	Ireland	NCT04780893
	Modius Spero active device	USA	NCT05242367
NightWare	Modius Spero active device	USA	NCT04040387
	NightWare Therapeutic System	USA	NCT03828656
HealthTech Connex Inc	Translingual neurostimulation	Canada	NCT05112003
Apollo Neuroscience, Inc	Apollo Wearable	USA	NCT05274230
Lifespan	Transcranial magnetic stimulation	The Netherlands	NCT05512143
Nu-Life Solutions	Nu-V3	USA	NCT05394545
Wave Neuroscience	Biometrics-guided Magnetic e-Resonance Therapy Completed study	USA	NCT02268084
	Biometrics-guided Magnetic e-Resonance Therapy	USA	NCT02990793
GrayMatters Health Ltd	Process-Instructed Self Neuromodulation ("Prism") Completed study	Israel	NCT04891614

Below are listed the **industrial sponsors,** currently having at least one clinical trial in progress **on "behavioral"** and PTSD (1 trial):

Industrial sponsor name	Behavioral	Country	NCT number
Big Health Inc.	Digital Cognitive Behavioral Therapy for Veterans	USA	NCT03688763

Below are listed the **industrial sponsors,** currently having at least one clinical trial in progress **on "other intervention"** and PTSD (2 trials):

Industrial sponsor name	Other intervention	Country	NCT number
Endominance Inc.	The Effects of Stress & Irregular Shift Hours on First Responders	USA	NCT05659277
WILD 5 Wellness**	Psychedelics and Wellness Study	USA	NCT04040582

** non interventional study, questionnaire on population is adults ages 18 and older that have taken a psychedelic at least once

The vast majority (94%) of ongoing clinical trials on PTSD are academics.
Among the 6% led by industrial sponsors:

- **69% (25/36) are conducted on molecule,**
- **22% (8/36) are performed on medical device,**
- **only 1 (3%) is conducted on behavioral therapy,**
- **the distribution is the same as last year.**

1.4.2. Molecules studied on ongoing clinical trials

Currently, **100** (vs 81 last year) clinical trials on PTSD are conducted on **molecule(s)**:

- **77%** (76) are conducted only on molecule(s),
- **23%** (24) are conducted by combining molecule(s) with behavioral management.

The following table presents all ongoing clinical trials conducted on molecule(s):

	Number of ongoing trials (Feb. 2023)
Molecules currently most studied (all molecules known),	
With or without combination with behavioral therapy	
MDMA	11
Ketamine	9
Cannabidiol (CBD)	7
Propanolol	6
Psilocybin	6
Known molecules currently being studied,	
with or without combination with behavioral therapy (depending on studies)	
Estradiol	2
Oxytocin*	2
Topiramate	2
Known molecules currently being studied, alone,	
without combination with behavioral therapy	3
Brexpiprazole & Sertraline	3
Dronabinol	3
Prazosine	2
Brexanolone*	2
Clonidine	2
Hydrocortisone	2
Methylphenidate	2
Pimavanserin	1
Bupivacaine*	1
Buprenex & Vivitrol *	1
Dexmedetomidine & Midazolam	1
Doxazosin*	1
Fluoxetine & Vilazodone*	1
Glecaprevir & Pibrentasvir*	1
Insuline	1
Lévodopa	1
Lipopolysaccharide*	1
Lofexidine & Buprenorphine	1
Pramipexole*	1
Pregnenolone	1
Quetiapine	1
Sertraline	1
Trazodone & Eszopiclone & Gabapentin	
Known molecules currently being studied,	
in combination with behavioral therapy	1
Allopregnanolone	1

Buprenorphine *	1
D-cycloserine	1
Dexmedetomidine*	1
Eszopiclone*	1
Fluoxetine*	1
Pregabalin	
New molecules being currently studied, alone, **without combination with behavioral therapy**	
Balovaptan*	1
BNC210	1
BI 1358894	1
CORT108297	1
JPZ150	1
Lu AG06466	1
NBTX-001*	1
NYX-783	1
TNX-102 SL*	1

**Was not tested in clinical trial last year*

Table 5: Presentation of molecules in ongoing clinical trial on PTSD

Molecules currently most studied in clinical trial on PTSD are dispatched as follow:
- 24 trials on psychotropic molecules (MDMA, Cannabidiol (CBD) and Psilocybin),
- 15 trials on well-known molecules (Ketamine and Propanolol).

Three are 3 categories of **known molecules**:

- newly registered in an ongoing clinical trial in 2023: Oxytocin, Brexanolone, Buprenex & Vivitrol, Doxazosin, Fluoxetine & Vilazodone, Glecaprevir & Pibrentasvir, Lipopolysaccharide, Pramipexole, Buprenorphine, Dexmedetomidine, Eszopiclone and Fluoxetine,
- always in an ongoing clinical trial in 2023,
- no more registered in an ongoing clinical trial in 2023: Escitalopram, Nitrous oxide, Bupropion and Paroxetine.

There are 3 categories of **new molecules**:

- newly registered in an ongoing clinical trial in 2023: Balovaptan, NTBX-001 and TNX-102 SL. Balovaptan is totally new in 2023 whereas NTBX-001 and TNX-102 SL had already been tested in previous clinical trials and consequently have been identified during our previous search last year,
- always in an ongoing clinical trial in 2023: BI 1358894, BNC210, CORT108297, JPZ150, Lu AG06466, NYX-783,
- no more registered in an ongoing clinical trial in 2023: ALTO-100 and 1 biomarker: [11C]MK-3168. ALTO-100 is now registered in ongoing studies on Major Depression Disease.

The following figure presents the number of ongoing clinical trials per molecule, in combination or not with behavioral therapy:

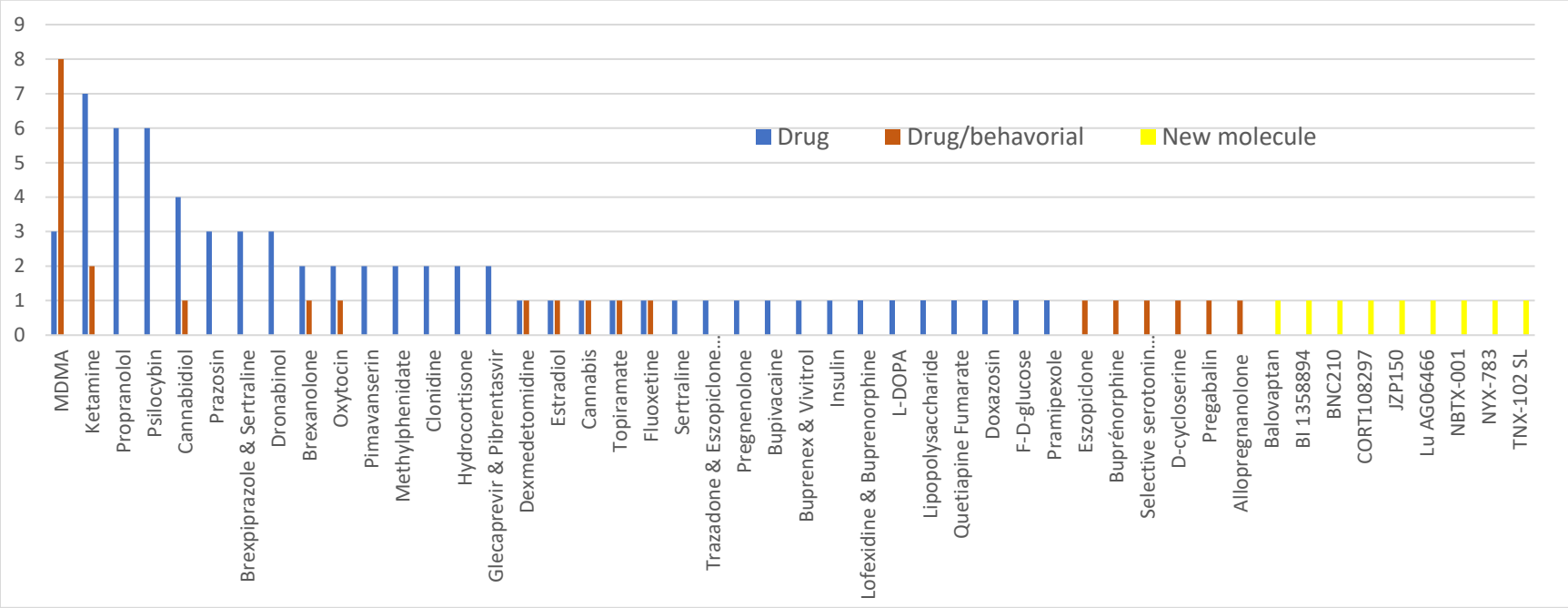


Figure 11: Ongoing clinical trials conducted on a molecule for the management of PTSD

Among the 9 new molecules in ongoing clinical trial on PTSD:
- 1 was not identified last year,
- 2 were not in ongoing clinical trial last year,
- all are under development by a private company,
- 8 have a clinical trial whose sponsor is industrial,
- 1 is in a clinical trial sponsored by the VA Office of Research and Development (CORT108297, developed by Corcept Therapeutics)

2. PTSD industrial players in clinical phase

The following table resumes all new molecules identified to be tested in PTSD indication, and the status of the tested molecules:

New molecule/biomarker to consider	**Society**	**Type of company**
ALTO-100	Alto Neurosciences	Start-up
Balovaptan	Hoffmann-La Roche	Major
BI 1358894	Hydra Biosciences/Boehringer Ingelheim	Major
BNC210	Bionomics	Start-up
[11C]MK-3168 (biomarker)	Bristol Myers Squibb	Major
CORT108297	Corcept Therapeutics	Biotech
JPZ150	Jazz Pharmaceutical	Biotech
LuAG06466	Lundbeck	Major
NBTX-001	Nobilis Therapeutics	Start-up
NYX-783	Aptinyx	Start-up
PT-150*	Pop Test & Palisades Therapeutics Companies*	Start-up
SRX246	Azevan Pharmaceuticals	Start-up
TNX-102-SL	Tonix Pharmaceuticals	Start-up
New molecule "abandoned"		
AZD6765 (Lanicémine)	Astra Zeneca	Major
GSK561679 (Verucerfont)	GSK	Major
Orvepitant	GSK	Major
PF-04457845	Pfizer	Major
Pomaglumetad Methionil	Eli Lilly	Major
PRAX 114	Praxis Precision Medicines	Start-up
PRX-03140	Predix Pharmaceuticals	Start-up
SNC-102	Synchroneuron	Start-up
SYN117	Biotie Therapies	Start-up
TTI-0102	Thiogenesis Therapeutics Inc.	Start-up

* CEO (Randi Altschul) involved in many diverse and varied non-medical structures, questioning the seriousness of society and molecule

Table 6: List of companies working on the 23 new molecules identified for the management of PTSD.

The following table presents the active companies working on new molecules to be considered according to their portfolio of molecules:

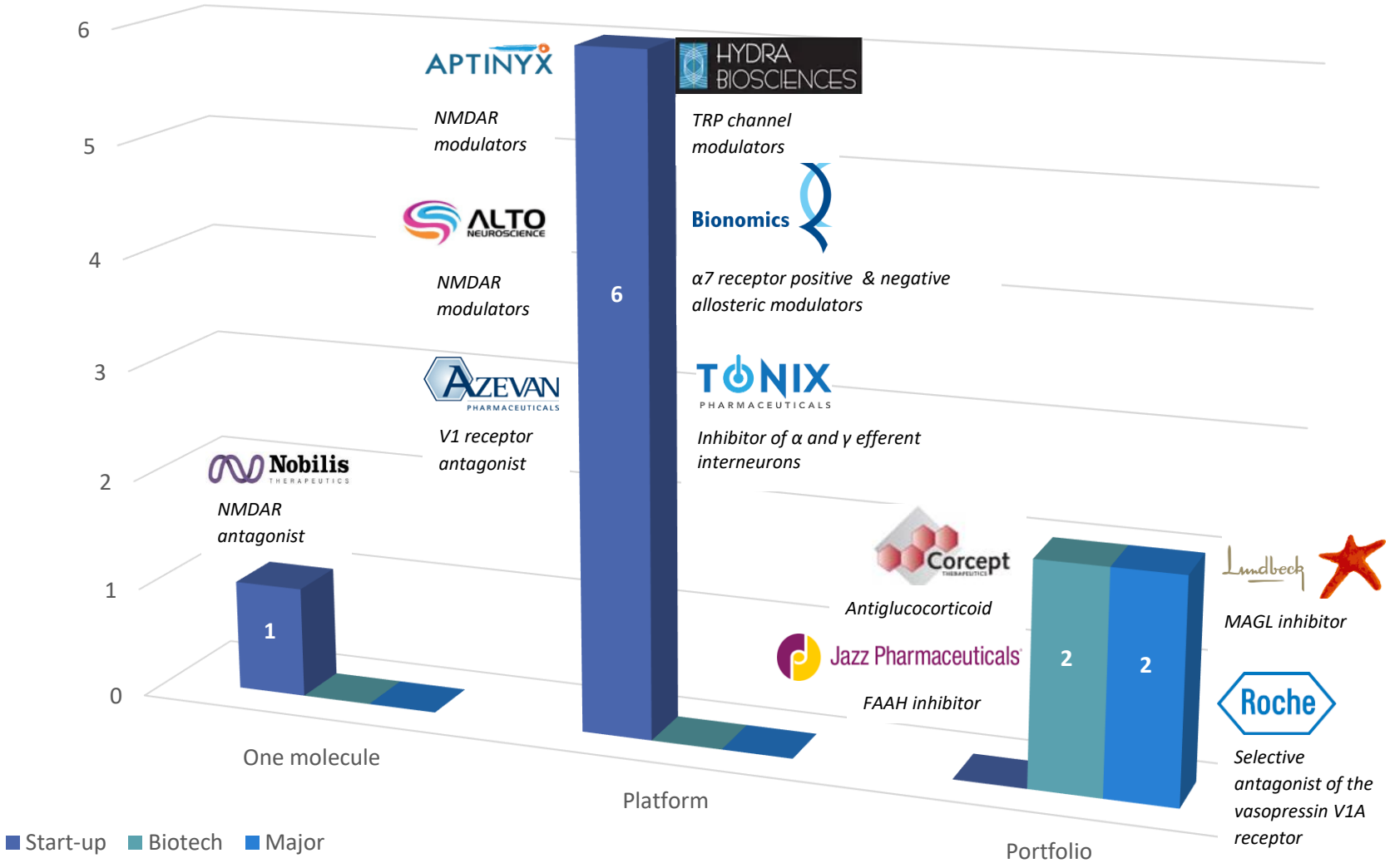


*Figure 12: Distribution of the 11 **active** companies working on new molecules to be considered according to their portfolio of molecules.*

2.1. Start-ups

Startups actives

(Ranking in descending order - funding height)

- **Aptinyx** (USA)
  - 51-100 employees, created in 2015, listed on the stock exchange in 2021,
  - Total amount of financing $268.3M, Série A 2016 ($65M), series B 2017 ($70M), then 3 post-IPO financing operations: January 2020 ($35M), October 2020 ($48.3M), September 2021 ($50M),
  - Molécules NYX-2925, NYX-783, NYX-458 **(NMDAR modulators),**
  - 1 ongoing Phase 2 study on **NYX-783** (PTSD), 1 ongoing Phase 2 study on NYX-458 (Parkinson's and Lewy dementia) and 1 ongoing Phase 2 study on NYX-2925 (fibromyalgia and diabetic pain).
- **Tonix Pharmaceuticals** (USA)
  - 11-50 employees, created in 2007, IPO in 2012,
  - Total funding amount $227.8M,
  - CNS indications and immunology (fibromyalgia, PTSD, MDD, covid-19, AUD, cocaine intoxication, organ transplantation, Prader-Willi syndrome),
  - **TNX-102-SL** molecule in PTSD **(decreased activity of alpha and gamma efferent interneurons),**
  - 4 phase 3 studies finalized on TNX-102-SL (PTSD), planning of 1 phase 2 study (adults, elderly, in Kenya in June 2022) (NCT05372887).
- **Bioxcel Therapeutics Inc** (USA)
  - 101-250 employees, created in 2017, listed on the stock exchange in 2018,
  - Total financing amount $140M, post-IPO equity 2022 ($5M+$135M),
  - 1 ongoing PTSD trial with **Dexmedetomidine** (repositioning),
  - Pipeline in neurosciences (AD and MDD -> BXCL501; severe acute agitation; chronic agitation in dementia; pre and post agitation in dementia) and immuno-oncology.
- **Alto Neurosciences** (USA)
  - 11-50 employees, created in 2019,
  - Total funding amount $40M, Series A 2019 ($8M), Series B 2021 ($32M),
  - Perpetual, non-exclusive license agreement with Total Brain Limited in Dec 2021 that will provide Alto Neurosciences with data from its international study to predict optimized treatment for major depression ($500,000),
  - Molecules Alto 100, 101, 102, 103, 104: cognition targeting; molecules Alto 202, 203, 204, 205, 206: emotion targeting, Alto 300: sleep targeting **(NMDAR modulators**),
  - 7 molecules at stage 1: Alto 102, Alto 103, Alto 104, Alto 203, Alto 204, Alto 205, Alto 206,
  - the phase 2 study on PTSD has just terminated in dec. 2022. 1 phase 2b study in progress on **ALTO 100 indication MDD and** 1 phase 2 study in progress on ALTO-300 in MDD.
- **Avezan Pharmaceuticals** (USA)
  - > 5 employees,
  - SRX228, SRX246, SRX251, SRX296 et SRX576 **(V1a receptor antagonist**, blocks effects of Arginine Vasopressine),
  - 3 phase 2 studies on **SXR246** (1 terminated on PTSD for funding, 1 finalized on Intermittent explosive disorders, 1 finalized on irritability Huntington's disease), no ongoing study with SRX246.
- **Nobilis Therapeutics** (USA)
  - 11-50 employees, created in 2015,

- Angel-Backed: angel 1 in 2016, angel 2 in 2018 ($500K),
- Molecule **NBTX-0001** (Xenon gas, **NMDAR antagonist**),
- Psychiatric treatments (PTSD and panic disorder) and neurodegenerative diseases (PKD, AD, ASD, OCD, IBS),
- 1 phase 2B study on PTSD ongoing, 1 phase 2B study on PD ongoing, PKD in phase 1, other preclinical stage indications.

Collaborations (with a large group or not)

- **Wild Health** (Australia)
  - 101-150 employees,
  - Health technology company designed around genomics-based medicine,
  - 1 ongoing trial on PTSD: **ketamine** in collaboration with True diagnostic (research, development, and manufacturing company specialized in immunodiagnostic test systems).
- **Bionomics** (Australia)
  - 11-50 employees, created in 1996, added to the stock market in 2021,
  - Total financing amount $38.6M, post IPO equity 2009 $10.1M, 2012 $10.4M, 2021 $18.1M,
  - Acquisition of Prestwick chemical (CRO Alsatian clinical trials) for €270,000 in 2014 -> recovery of the partnership between the CRO and Merck&Co, sold in March 2020 to Domain Therapeutics,
  - Acquisition of Neurofit (CRO preclinical trials on the CNS in Alsace) for €1.25M in 2005, sold in March 2020 to Domain Therapeutics,
  - Clinical stage molecules: **BNC210** (**selective negative allosteric modulators of the α7 receptor**) on PTSD and SAD, BNC375 (**α7 receptor positive allosteric modulators**) on AD and others CNS diseases. Molecules preclinical stage: activators of potassium channels Kv3.1/3.2 for the treatment of schizophrenia, autism, cognitive deficits; inhibitors (with functional selectivity) of sodium ion channels voltage dependent Nav1.7 and Nav1.8 for chronic pain without the risk of dependence associated with opioid treatment,
  - Partnership with Merck&Co in 2014: BNC375 on AD and other CNS conditions. Initial payment of US$20M then US$10M for Phase 1 in 2017. The deal is valued at US$506M in upfront, research and milestone payments achieved + additional royalties on net sales of licensed products and could receive up to US$465M in additional payment for certain development and commercial milestones,
  - Partnership with Merck Serono in 2008: Kv1.3 on multiple sclerosis. Initial payment of US$2M and funds for the research program. Merck Serono is funding all development, including clinical development. For each compound selected by Merck Serono, additional payments to be received, up to US$47M if the selected compound is successfully developed and marketed. In addition, royalties collected (rate not made public) on net sales of licensed products,
  - Partnership with Carina Biotech in 2020: BNC101 on the treatment of advanced colorectal cancer (preclinical stage),
  - Partnership with Empath Bio in 2021: combination of BNC210 and MDMA molecules for PTSD (pre-linear stage),
  - 1 ongoing Phase 2b study on PTSD (BNC210), 1 ongoing Phase 2 on SAD (BNC210), 1 ongoing Phase 1 study on AD (BNC375).

Startup/ molecules acquired

- **ATAI Life Sciences** (Germany):
  - 81 employees, created in 2018, entry on the stock market in 2021, turnover in 2021 $20M,

  - Total financing amount $347.1M, series A 2018 ($25.5M), B 2019 ($43M), C 2020 ($93M), D 2021 ($157M),
  - Acquisition of Perception Neuroscience in 2019, which develops PCN-101 (Arketamine, or R-ketamine) in severe mental disorders,
  - Spinout EntheogeniX Biosciences with Cyclica Inc in 2019 (using AI and computational biophysics to discover new psychedelic-based drugs),
  - Launch of the **subsidiary Empath Bio** (2020): development of **MDMA** derivatives with different pharmacological profiles of MDMA (separation of the entactogenic effects of MDMA from certain known adverse reactions) to treat PTSD and other indications,
  - Acquisition **Halucenex Life Sciences Inc** (2021): psychedelic medicine, focus on Veterans (CEO is a veteran), **MDMA** on PTSD (LSD and psilocybin on anxiety, depression, alcoholism),
  - Equity stake increase in **COMPASS Pathway** (nov 2021): **psilocybin** on PTSD (and MDD, TRD, …).
- **Hydra Biosciences** (USA)
  - 11-50 employees, created in 2001, IPO in 2019,
  - Total funding amount $94.9M, Series A in 2002 ($9.3M) (start-up stage), Series B in 2004 ($18.9M) (start-up stage), Series C in 2008 ($34M) (start-up stage), Series D in 2009 ($22M) (generating revenues), Series E in 2015 ($$ 10.5M) (generating revenues) for Phase I trials,
  - Acquisition by Eli Lilly in 2018 for $22.6M,
  - Partnership with **Bohringer Ingelheim** in 2015 on "renal disease and disorders" – 2 molecules,
  - Acquisition by Elli Lilly in 2018 "preclinical pain program" – all active ingredients related to the preclinical program on TRPA1 antagonists, part of the TRP family of ion channels, under study for the treatment of chronic pain syndromes,
  - Activities on pain, inflammation, anxiety, cardio; 6 indications. Molecules targeting ions channels (**TRP channel modulators**) including **BI135886**, HX-100. HX-100 is a TRPA1 modulator for diabetic neuropathy and allergic asthma (phase 1). Other preclinical programs for dermatological disorders and pulmonary fibrosis.

Molecules whose development seams on hold or suspended

Regardless of the status of the company, the molecules that were being developed by these companies are not found and therefore considered abandoned.

- **Synchroneuron** (USA) created in 2011, total amount of funding $26M, series A in 2012 ($6M), series B in 2014 ($20M) (phase 1 PTSD, phase 2 tardive dyskinesia and Tourette syndrome), studies withdrawn, funding stopped, start-up closed (molecule SNC102).
- **Biotie Therapies** (Finland), total funding amount $252.5M, acquired in 2016/ Acorda Therapeutics (USA), no mention of the SYN117 molecule, nor PTSD in the pipeline.
  - **Acorda Therapeutics** (USA), (between 251 and 500 employees), IPO 2007, CA 2020 $153M, total funding amount $156.6M:
    - Products with marketing authorization: AMPYRA (dalfampridine) to improve walking in people with multiple sclerosis and INBRIJA (levodopa inhalation powder) for OFF episodes of PK patients treated with regular carbidopa/levodopa medicines),
    - Development rHIgM22, remyelinating antibodies for multiple sclerosis and GGF2, neureguline growth factor, promotes recovery after neurological injury.
- **Predix Pharmaceutical** (USA), total financing amount $54.6M, acquired in 2006/ Epix Pharmaceutical (USA), liquidation in 2009 (PRX-03140 molecule).

- **Thiogenesis Therapeutics Inc** (France) created in 2017 by Charles Rioux, no activity for 3 years, became an investment fund (molecule TTI-0102).
- **Praxis Precision Medicines** (USA)
  - 139 employees, created in 2015, listed on the stock exchange in 2020,
  - Total funding amount $223.1M: Series A 2016 ($3.1M), Series B 2018 ($18.8M), Series C1 2020 ($110M), post-IPO equity 2021 ($91.3M),
  - Molecules in psychiatry: **PRAX-114**: terminated study (no longer developing for PTSD indication), ongoing registrations on MDD (**GABAA receptor positive allosteric modulator**), PRAX-040 in the preclinical stage,
  - Molecules on epilepsy (PRAX-090, PRAX-020, PRAX-222, PRAX-100, PRAX-628, PRAX-562, PRAX-030, PRAX-080) and movement disorders (**PRAX-114**, PRAX-944, PRAX-050).

2.2. Biotechs/Mid-sizes

- **Sage Therapeutics** (USA)
  - 501-1000 employees, created in 2010, listed on the stock exchange 2014, TR 2022 $7.7M,
  - Total funding amount: $2.7B. Series A 2011 $35M, Series B 2013 $20M, Series C 201$4 $38M, post-IPO equity 2015 $138M, 2016 $150M+$175M, 2017 $345M, 2018 $575M, 2019 $575M, 2020 $650M,
  - PTSD studies with **Brexanolone** (Zulresso®) already approved on postpartum depression,
  - Therapeutic axes: depression, neuropsychiatry (AD, PD, ...), preclinical in progress on NMDA hypofunction and GABA hypofunction.
- **Corcept Therapeutics** (USA)
  - 238 employees, created in 1998, TR 2022 $404M,
  - Molecules CORT-125134 (Relacorilant), CORT-125134 (Miricorilant), CORT-125281 (Exicorilant), CORT-108297, CORT-113176 (non-steroidal compounds, cortisol modulator at glucocorticoid receptor -> antagonist of glucocorticoid receptor -> **antiglucocorticoid**) or RU 486 – Mifepristone – progesterone structural analogue,
  - Endocrine & metabolic, oncological, neurological, addiction, ophthalmological and psychiatric activities, related to excess cortisol,
  - 1 ongoing Phase 2 study on **CORT-108297** (PTSD) sponsored by the VA Office of Research and Development, 1 ongoing Phase 1 study on CORT-113176 (Amyotrophic lateral sclerosis), multiple studies on other molecules.
- **ACADIA Pharmaceutical Inc** (USA)
  - 514 employees, created in 1993, listed on the stock exchange in 2013, TR Q1-Q3 2022 $38.7M,
  - Activity on CNS: Parkinson, AD, Rett syndrome, schizophrenia, postoperative pain and osteoarthritis,
  - 1 ongoing Phase 4 study on **Pimavanserin** (**5HT-2a serotonergic receptor specific inverse agonist**) in the treatment of PTSD insomnia in veterans, already marketed under the name Nuplazid® for the treatment of hallucinations and delusions in Parkinson disease. In addition, several studies are underway on Parkinson, neurodegenerative diseases and schizophrenia.

2.3. Major

- **Lundbeck** (DK)
  - 5600 employees, created in 1915, CA 2022 $2.61B,

  - Activities in neurology (AD, PD, migraine, neuropathic pain, Tourette syndrome), psychiatry (indications: bipolar disorders, borderline personality disorders, anxiety disorders, depression, PTSD, schizophrenia),
  - Focus PTSD: 2 molecules:
    - Partnership with Otsuka Pharmaceutical Development & Commercialization, Inc. on **Brexpiprazole** (**serotonin-dopamine activity modulator**: partial agonist serotonin receptor 5-HT1A and dopamine D2 receptor and serotonin 5-HT2A receptor antagonist and α1B/α2C norepinephrine receptors). Marketed under the name Rexulti® for the treatment of schizophrenia. 3 phase 3 studies in progress on PTSD.
    - **Lu AG06466** (**specific inhibitor of monoacylglycerol lipase (MAGL),** enzyme responsible for the degradation of the 2-AG endocannabinoid ligand, improving the actions of 2-AG on CB1 and CB2-> receptors restores neuronal transmission and decreases neuroinflammation). 1 ongoing phase 1 study.
- **Jazz Pharmaceutical PLC** (USA)
  - 3200 employees, created in 2003, listed on the stock market 2012, TR 2022 ¤3.65B,
  - Acquisition in 2021 of GW Pharmaceuticals for $7.2 Billion (specializing in the development of cannabinoid drugs, one of the leading producers of medical cannabis in the world). Epidiolex® in multiple sclerosis, epilepsy or Lennox-Gastaut syndrome generated $511M in 2020,
  - Acquisition in 2020 of Springworks Therapeutics for a first payment of $35M with a potential payment of up to $375M depending on clinical advances. Acquisition of "FAAH inhibitor program" with the molecule PF-04457845, including the license agreement signed in 2017 between Springworks and Pfizer,
  - 2016 Acquisition of Celator Pharmaceuticals for $1.5 Billion, specializing in Leukemia treatment,
  - Molecules in:
    - Neurosciences: JPZ324, JPZ385, **JPZ150** (PTSD: **highly selective inhibitor of the enzyme fatty acid amide hydrolase (FAAH)**),
    - Oncology: JPZ341, JPZ815, JPZ351, Lurbinectedin, JPZ458 (Rylaze®: MA for hypersensitivity to E. coli derived from asparaginase treatments),
    - Schizophrenia: cannabinoids.
- **Boehringer Ingelheim** (Germany)
  - 52 000 employees, created in 1885, TR Q16S2 2022 €11.2B,
  - 1 ongoing trial **BI 1358894** in phase II in PTSD.
- **Bristol Myers Squibb** (USA)
  - 32 000 employees, created in 1989 from Bristol Myers and Squibb merger, CA 2022 $46.4Md,
  - ongoing study on the biomarker **[11C]MK-3168** tested on healthy volunteers (phase I) with the drug CC-97489 and the drug [18F]T-401 in Belgium (Leuven). Feasibility pilot has been completed last year (PTSD, AU disorder and Psychosis are targeted).
- **Pfizer** (USA)
  - 92 000 employees, created in 1849, TR 2022 $100.3B,
  - 1 ongoing trial **Dexmedetomidine vs Midazolam** in PTSD.
- **Hoffmann-La Roche** (Switzerland)
  - 100 000 employees, created in 1896, TR 2022 $68.55Md,
  - 1 ongoing trial on drug **Balovaptan** (**selective small molecule antagonist of the vasopressin V1A receptor** which is under development by Roche for the treatment of autism. As of August 2019, it is in

a phase III clinical trial for adults and a phase II clinical trial for children for this indication) in phase II in PTSD.

Two molecules, belonging to "major" companies have obtained a Market Authorization in the management of PTSD (more precisely management of depression associated with PTSD):

Laboratory	GSK/Chiesi	GSK
DCI	Sertraline	Paroxetine
Name FR	Zoloft	Deroxat/Divarius
Nom USA	Zoloft	Paxil
AMM ANSM	16-jan-96	24-jun92
AMM FDA	1991	1992
AMM PTSD	2-Feb-00	6-dec-01
Income peak	$3.4 billion (2004)	$2.7 billion (2002)

Table 7: General data on molecules7 having a market authorization in PTSD

In the management of PTSD,
- 1 major company (Hoffmann-La-Roche) is newly identified this year in the clinical development of a new molecule,
- 8 start-ups, 2 biotechs and 3 major companies are identified as especially active in the clinical development of a new molecule (12 new molecules and 1 biomarker in development),
- 3 start-ups are closed, 4 start-ups were acquired by a major pharma,
- 2 molecules, Sertraline and Paroxetine, obtained a market authorization (for the management of depression associated with PTSD) mid of 90s in a major group (GSK), with an income pick of $3.4billion and $2.7billion, respectively.

3. Intellectual Property in PTSD

The method of search is defined in annex 5.

On the 567 patents identified, 548 (96.6%) were identified as relevant, only 19 being not related to PTSD.

The following table shows results of patent analysis:

CATEGORY		ASSIGNEE	TOTAL	TOTAL (%)
API	NARCOTICS	ACADEMIC	9	13 (2.4%)
		INDUSTRIAL	3	
		INDIVIDUAL	1	
	NON-NARCOTICS	ACADEMIC	108	433 (79%)
		INDUSTRIAL	310	
		INDIVIDUAL	14	
		PATENT LAYER	1	
OTHER		ACADEMIC	45	102 (18.6%)
		INDUSTRIAL	32	
		INDIVIDUAL	24	
		NO ASSIGNEE	1	
				548

* Results on 26.5 years, excluding the last 18 months

Table 8: 548 patents particularly targeting PTSD filed over the last 25 years

A large majority of patents (78.7%) concern API and are deposed by an industrial in 72% (310) of case.

The top five of industrial patent applicants on PTSD are presented in the following table:

Top five of industrial assignee	Total number of patents filed targeting PTSD
Pfizer	53
Roche	29
Lundbeck	25
Bristol Myers Squibb	20
Taisho Pharmaceutical	18

Table 9: Top five of industrial assignee targeting PTSD

All industrial assignee in top five are major pharmaceutical companies, with Pfizer and Lundbeck identified with ongoing clinical study(ies) on PTSD.

Considering start-ups and biotech companies in clinical phase on PTSD (identified in section 2), number of filed patents are presented in the following table. Only companies for which at least one patent filing has been identified are listed in the table.

Start-ups and biotechs	Total number of patents filed targeting PTSD
Tonix Pharmaceuticals	4
Jazz Pharmaceuticals	2
Corcept Therapeutics	2
Synchroneuron	2
Biotie Therapies	2
ReST THERAPEUTICS	1
Acadia Pharmaceutical Inc	1
Aptinyx	1
Compass	1
Praxis Precision Medicines	1

Table 10: Start-up and biotech assignee in clinical phase targeting PTSD

With 4 patents filed targeting PTSD, Tonix Pharmaceuticals is the major applicant for start-ups. Synchroneuron has been closed without known acquisition of the company and Biotie Therapies was acquired by Acorda in 2016.

Aptinyx developing a molecule acting on NMDA as a positive modulator is the closest competition identified to ReST FENM and has one patent application targeting PTSD.

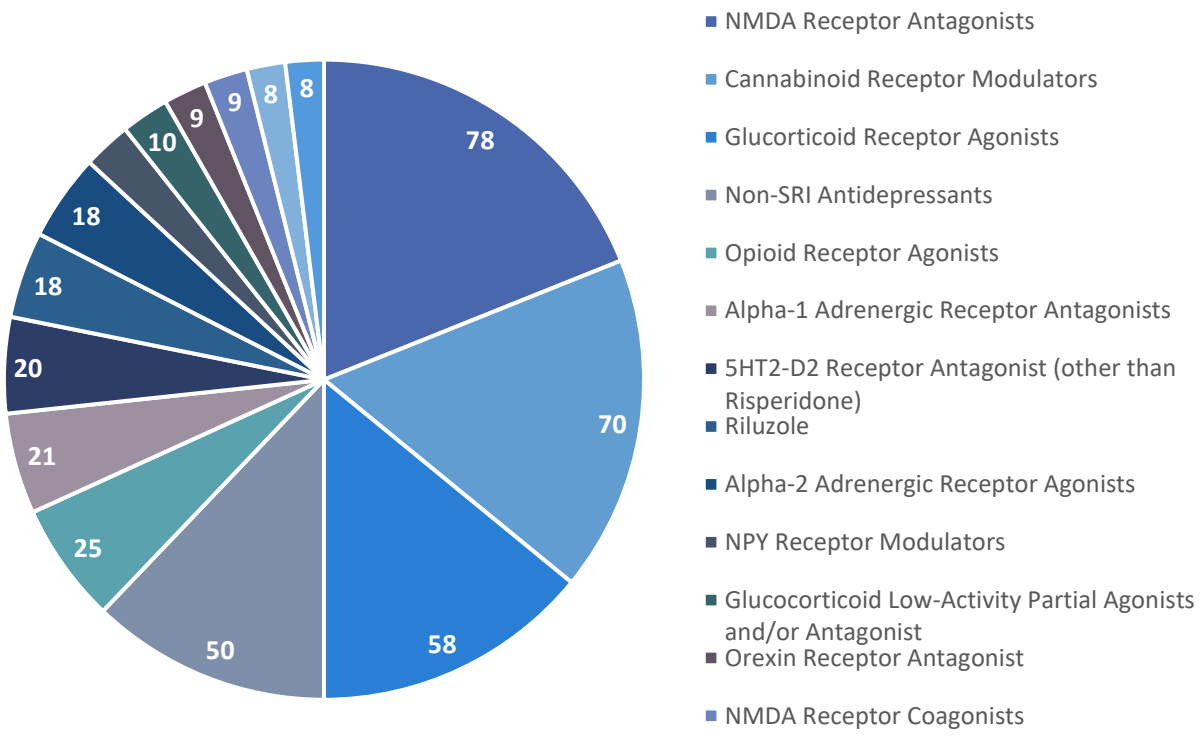
Considering start-ups developing a new molecule on PTSD, ReST Therapeutics is normally position on IP specifically targeting PTSD.

4. Global MAPPING of molecules for the management of PTSD

4.1. Top therapeutic targets for PTSD from expert group

Data from this section are issued of the article written by Krystal et al. and published in 2017 in Biological Psychiatry[1].

The top 10 recommendations for mechanisms are presented in the Table below. To generate data in this table, surveys was sent to 45 PTSD investigators around the world, chosen on basis of their involvement in previous VA, DoD, NIMH, and industry-sponsored PTSD clinical trials, and the PTSD Psychopharmacology Working Group, asking them to rank the top five potential new therapeutic targets for PTSD. The data were analyzed in a weighted fashion (eight points for top rank, five points for second, four points for third, three points for fourth, two points for fifth). Sixty percent (n=27) of the invitees completed the survey.



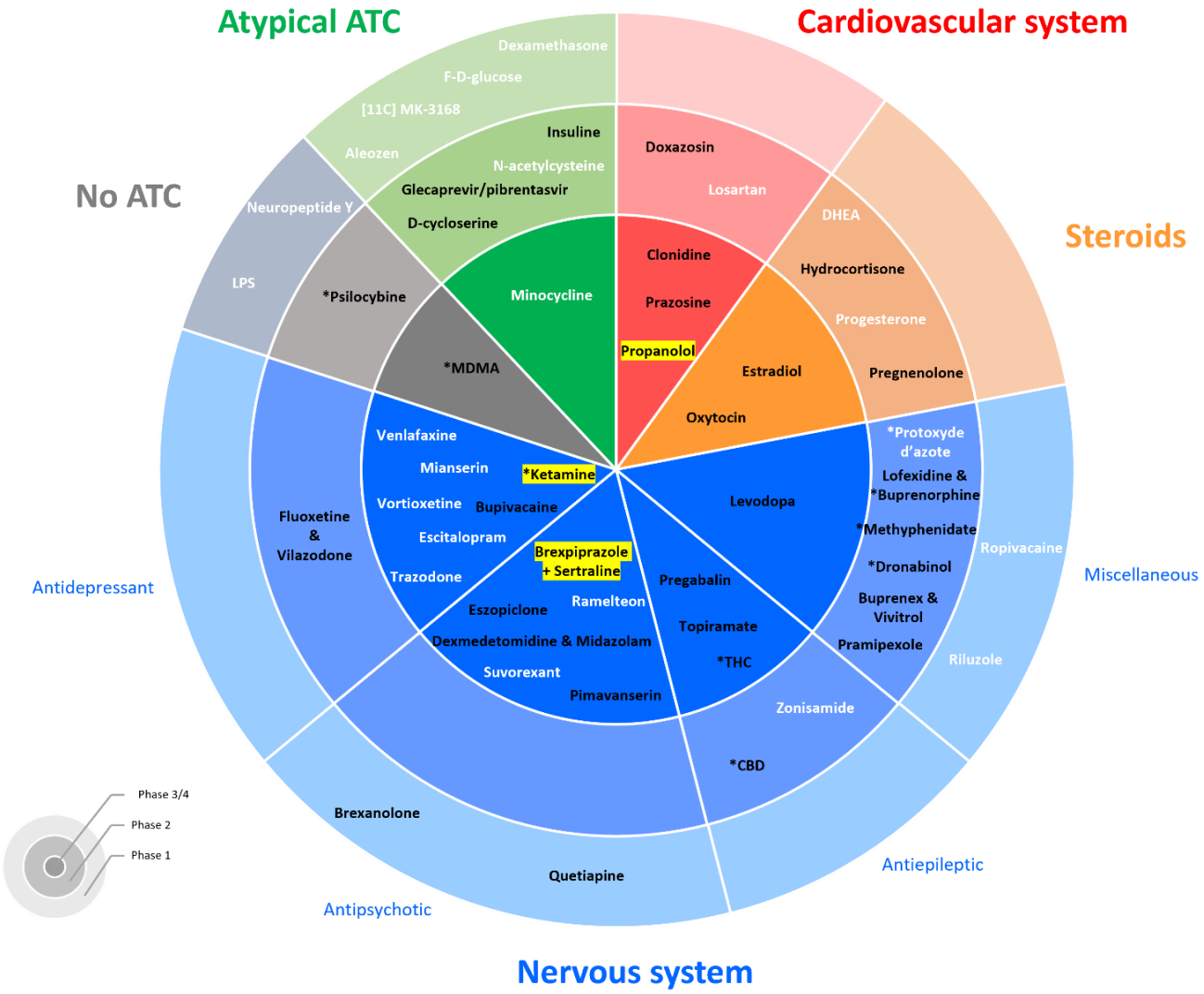
D2 : dopamine type 2; NMDA : N-methyl-D-aspartate; NPY: Neuropeptide Y; SRI: Serotonin reuptake inhibitor; 5-HT2: 5-hydroxytryptamine-2

Figure 13: top therapeutic target for PTSD from expert group

The top agents included rapid acting antidepressant mechanisms (ketamine-like drugs, scopolamine), cannabinoid drugs that might have anxiolytic effects or enhance extinction (cannabinoid receptor type 1 agonists, cannabidiol, fatty acid amide hydrolase inhibitors), glucocorticoid signaling, non-SRI antidepressants/monamine transporter antagonists (trazodone, vortioxetine, cyclobenzaprine, etc.), opioids (buprenorphine, kappa opioid receptor antagonists), riluzole, and other mechanisms. There are already completed or ongoing trials with several of these agents, including ketamine, glucocorticoids, and riluzole.

[1] http://dx.doi.org/10.1016/j.biopsych.2017.03.007

4.2. Molecules repositioned from an indication other than PTSD



Ongoing clinical study for molecules in bold

**Molecule considered as narcotic or subject to misuse and abuse*

Figure 14: Market authorization repositioning or extension molecules for the management of PTSD involved in a clinical trial since 2015

Over the period 2015 to today, **24 molecules** for repositioning or extending marketing authorization are in phase 3 clinical trial(s) on PTSD (molecules that do not get a market authorization and are registered in phase 4 are considered to be in phase 3):

1. **Brexpiprazole/Sertraline** and **Brexpiprazole/Propanolol**: Brexpiprazole is a derivative of Aripripazole (Abilify®, developed initially and mainly in the same indications (antipsychotic in schizophrenia; prevention and treatment of manic episodes in bipolar I disorder)) in the hope of being better tolerated with fewer side effects than the latter. Three ongoing studies sponsored by Otsuka Pharmaceutical. Otsuka Pharmaceutical has partnered with Lundbeck to develop its Brexpiprazole/PTSD research (see 2.3). The efficacy of Brexpiprazole

on PTSD is currently being studied in combination with Sertraline in 2 clinical studies and in combination with Sertraline and Propanolol in 1 study (see 1.4.1). Of the three previous studies conducted as part of their partnership, two were stopped prematurely and one showed a decrease in PTSD symptoms (CAPS-5) during Brexpiprazole/Sertraline administration2, suggesting a possibility of obtaining a market authorization in the treatment of PTSD.

In addition, Otsuka Pharmaceutical and Lundbeck have published an article on the economic data of PTSD in the United States, supporting their involvement in the management of PTSD and suggesting a potential solution in its treatment with significant economic benefits3.

2. **Ketamine**: historically (1969) at high dosage, it is an intravenous anesthetic agent called dissociative (alone in its class), without respiratory or cardiovascular depression (agent of choice in disaster medicine, war, or veterinary in natural environment – hypodermic darts); then at a much lower dosage (~10 times lower), anti-hyperalgic drug (preventive and curative) from the 2000s; and finally antidepressant from the 2010s (an MA for the S enantiomer in intranasal form Spravato® in 2019); NMDA receptor antagonist, known for its psychotropic psychodysleptic and hallucinogenic effects (recreational diversion), classified as narcotics; studied in the management of PTSD for many years: 2 phase 2 studies before 2015, 3 phase 3 studies since 2015.
3. **Propranolol** (Avlocardyl®, Inderal®): non-cardioselective peripheral blocker acting by blocking the action of adrenaline; off-label off-label off-label use fairly well accepted in prevention and treatment... stage fright, performance stress in front of an audience; studied for many years in the management of PTSD (several phase 3 and 4 studies before 2015, 3 phase 3 studies since 2015).
4. **Prazosin** (Alpress®, Minipress®): antihypertensive (alpha blocking α1 vasodilator peripheral and α 1 central receptors) studied for many years in the management of PTSD; several phases 2, 3 and 4 studies before 2015, 3 phase 3 studies since 2015.
5. **Pregabalin** (Lyrica®): initially an antiepileptic drug related to GABA, later used in the treatment of neuropathic pain and generalized anxiety disorder, only 1 Phase 3 study since 2015 listed in the PTSD (management of patients with alcohol dependence and PTSD).
   NB: as an example of the dosage adjustments and therapeutic windows of certain psychotropic drugs, Lyrica is marketed in the form of capsules with 25... and 300 (50 75 100 150 200) mg, the daily dosage ranging from 150 (sometimes less) to 600mg in 2 or 3 doses.
6. **Estradiol**: natural sex hormone (estrogen), therapeutic use (in combination) as a contraceptive and in Hormone Replacement Therapy. Was studied in a Phase 3 study prior to 2015 and is currently in 1 Phase 3 study and then Phase 1 study.
7. **MDMA**: psychostimulant molecule of the amphetamine class ("ectasy") with entactogenic effects, studied for many years in the management of PTSD: 10 phase 2 studies before 2015, 1 phase 3 study and several phase 2 and phase 1 studies since 2015. MAPS PBC recently announced[4] that its confirmatory phase 3 MAPP2 trial of MDMA-Assisted Psychotherapy was positive and that it will submit a NDA to the FDA in Q3 2023, precise results are not yet published nor available5. The study met both the primary endpoint as measured by the change from baseline in Clinician-Administered PTSD Scale for DSM-5 (“CAPS-5”) and the key secondary endpoint of improvement in functional impairment associated with PTSD as measured by the change from baseline in the Sheehan Disability Scale (“SDS”). No serious adverse events were observed.

[2] for details, see https://www.clinicaltrials.gov/ct2/show/results/NCT03033069

[3] https://www.psychiatrist.com/jcp/trauma/ptsd/economic-burden-posttraumatic-stress-disorder-united-states-societal-perspective/

4 https://www.clinicaltrials.gov/ct2/show/NCT04077437

5 https://mapspublicbenefit.com/press-releases/maps-pbc-announces-positive-results-from-confirmatory-phase-3-mapp2-trial/

8. **Trazodone** (Trazolan®, Oleptro®, Desyrel®): antidepressant, highly sedative for insane patients and agitated Parkinson's patients, poorly known target adrenergic and dopaminergic and antagonist of the 5-HT2A receptor. No study before 2015, 1 study in phase 3 then 1 in phase 1 since 2015.
9. **Dexmedetomidine** (Dexdor®) **/ Midazolam**: sedative or even anesthetic drug and intravenous analgesic adrenergic agonist α_2A presynaptic central (and hypotensive via a lesser agonist effect on the central receptors α_2C). Currently 1 Phase 3 study, 2 Phase 1 studies have been conducted since 2015 and 1 Phase 1 study before 2015.
10. **Clonidine** (catapressan®): antihypertensive of central action (presynaptic central adrenergic agonist α_2C not very selective of the A/B/C subtypes) with sedative and analgesic collateral effects (α_2A receptor agonist). 1 single study (phase 3 ongoing) conducted in the management of PTSD.
11. **Suvorexant** (Belsomra®): sleeping pill, orexin receptor antagonists, used in the treatment of insomnia. 2 phase 3 studies since 2015.
12. **Venlafaxine**: antidepressant from the family of serotonin and norepinephrine reuptake inhibitors. 1 phase 3/4 study before 2015, 2 phase 3 studies since 2015.
13. **Pimavanserin** (Nuplazid®): Agonist specific to serotonergic receptors type 5HT-2a1, with little effect on 5HT-2c. Antipsychotic for the treatment of hallucinations and delusions associated with the psychosis of Parkinson's disease. 2 phase 3 studies since 2015.
14. **Oxytocin**: (Syntocinon®): octopeptide synthesized in the hypothalamus that stimulates milk emission and uterine contractions; hormone that behaves in the brain like a neuropeptide. Increases the frequency and intensity of uterine contractions. Used in the management of postpartum hemorrhagic uterine atonias, inductions of uterine retraction after obstetric surgery, insufficiency of uterine contractions during labor. 1 phase 3 study and 8 phase 2 studies since 2015.
15. **Vortioxetine** (Brintellix®): antidepressant, the mechanism of action would be related to the direct modulation of the activity of serotonergic receptors and the inhibition of the serotonin transporter (5-HT). Non-clinical data indicate a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, a partial 5-HT1B receptor agonist, a 5-HT1A receptor agonist, and a 5-HT transporter inhibitor, leading to neurotransmission modulation in several systems, and a Phase 3 study since 2015.
16. **Levodopa**: antiparkinsonian that belongs to the dopaminergic family; levodopa is transformed into dopamine in the body. 1 Phase 2 and Phase 1 Phase 3 study since 2015.
17. **Mianserin**: antidepressant, also has a tranquilizing and sedative effect. 1 of phase 3 since 2015.
18. **Minocycline**: antibiotic of the cyclin group, indicated against many bacterial infections, used mainly as an anti-acne. 1 of phase 3 since 2015.
19. **Ramelteon** (Rozerem®): a sleeping pill that selectively binds to MT 1 and MT 2 receptors 6 in the suprachiasmatic nucleus (SCN), instead of binding to GABA A receptors that are associated with anxiolytic, muscle relaxant, and amnesic effects. 1 phase 3 study since 2015, terminated prematurely for lack of response.
20. **Escitalopram** (Lexapro®, Cipralex®, Sipralexa®, Seroplex®) / Duloxetine: Escitalopram is a selective serotonin reuptake inhibitor antidepressant. Duloxetine is an inhibitor of both serotonin (5-HT) and norepinephrine (NA) reuptake. Used for the management of neuropathic pain of diabetics, major depressive episodes, generalized anxiety disorders. Combination of the 2 molecules studied in 1 Phase 3 study since 2015, terminated prematurely due to inability to enroll patients in a timely manner due to the COVID-19 pandemic.
21. **Eszopiclone** (Lunesta®): hypnotic, benzodiazepine-like properties, treatment of insomnia. 2 phase 3/4 studies before 2015, 1 phase 3 since 2015.

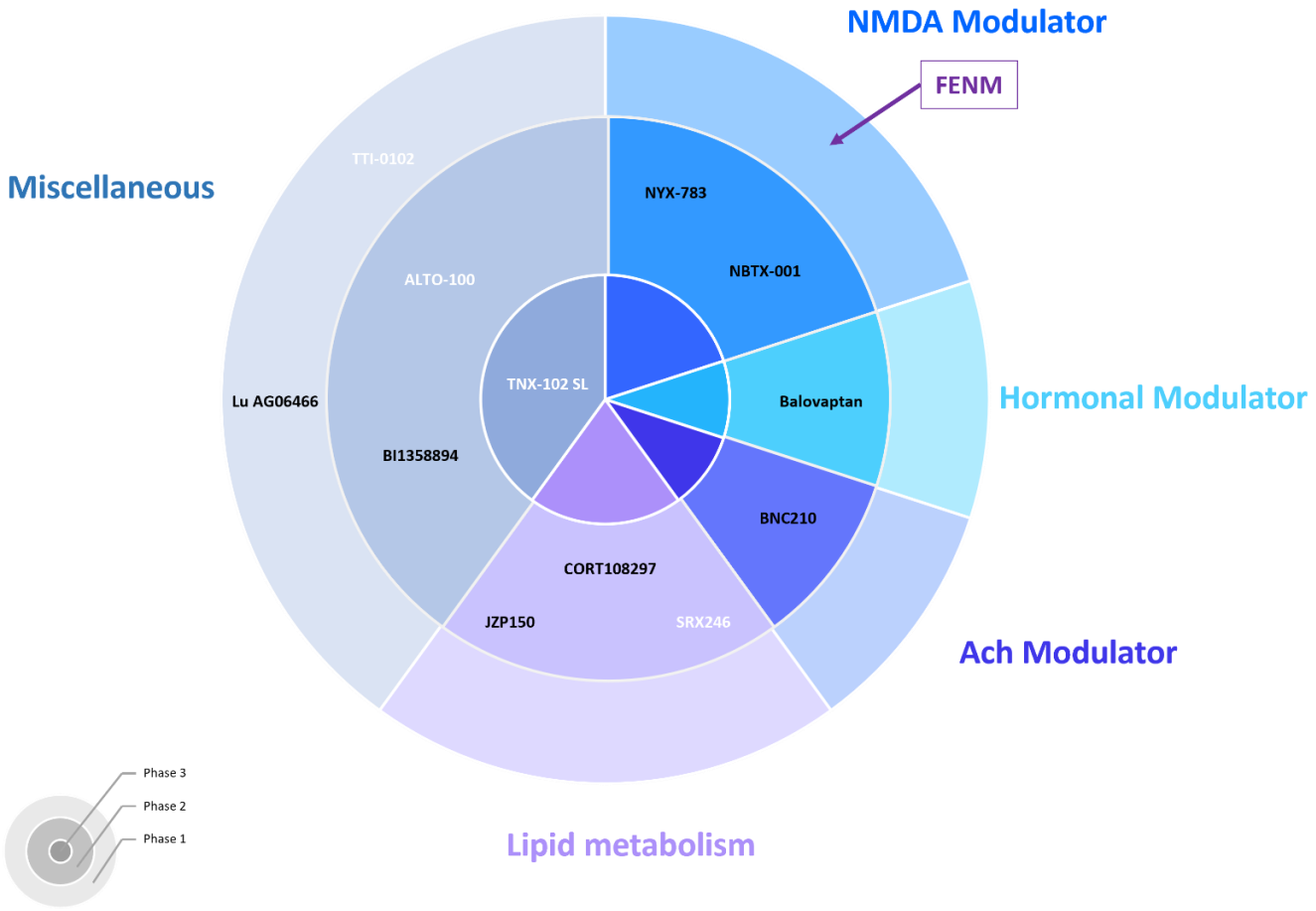
[4] https://en.wikipedia.org/wiki/Melatonin_receptor

22. **Topiramate** (Epotomax®, Topamax®): indicated for epileptic, migraine or Lennox-Gastaut syndrom. It increases the frequency with GABA activated GABAA receptor and increased the ability of GABA to induce the influx of chloride ions into neurons, suggesting that Topiramate potentiates the activity of this inhibitory neurotransmitter. 8 studies before 2015, 3 studies since 2015.
23. **THC** (Dronabinol®, Sativex®): cannabinoid, psychotic, acting on the psyche by modifying the cerebral rhythm. Anti-inflammatory properties. It is approved in more and more pharmacopoeias (DAB, USP ...) for various indications, such as appetite disorders, certain glaucoma, sedation, treatment of chronic pain (e.g. complications related to immunity disorders). It is mainly used against vomiting and nausea in cancer patients to alleviate the side effects of chemotherapy It is also used to increase appetite in AIDS patients. 2 studies before 2015, 12 studies since 2015.
24. **Bupivacaine** (Marcaïne®): strongest local anesthesic currently in use. Reserved for hospital use, it is indicated in spinal anesthesia, epidural anesthesia and certain peripheral blocks. 1 study before 2015 and 2 studies since 2015, used when the medical procedure Stellate Ganglion Block (SGB) is the intervention in studies on PTSD. SGS involves injection of a local anesthetic (a medication that causes reduced sensation/feeling in a given area) around the stellate ganglion, which is a collection of nerves near the base of the neck. This procedure causes a short-lived, temporary shutdown of nerve signals.

Among the repositioning molecules, Brexpiprazole (in combination with Sertraline) is the molecule considered to have the highest potential to obtain market authorization in the management of PTSD within a short period of time.

The following molecule could be MDMA-Assisted-Psychotherapy within the specific frame of Psychedelic-Assisted-Therapy.

4.3. New molecules



Ongoing clinical study for molecules in bold

Figure 15: New molecules involved in a clinical trial since 2015 for the management of PTSD

Over the period 2015 to today, **12 new molecules** are considered:

1. **ALTO-100**: Nonsteroidal anti-inflammatory drugs (NSAIDs). It works by inhibiting cyclooxygenase (COX 1 and 2).
2. **Balovaptan:** Selective small molecule antagonist of the vasopressin V1A receptor.
3. **BI 1358894:** Inhibitors of trpc4 and TRPC5 cationic channels (transient receptor potential canonical channels) that constitute a subfamily of non-selective calcium permeable cationic channels, which are involved in neural development, brain function and neurological diseases.
4. **BNC210:** Anxiolytic, negative allosteric modulator of the nicotinic alpha 7 receptor of acetylcholine involved in long-term memory and strongly expressed in the amygdala.
5. **CORT108297:** Selective glucocorticoid receptor antagonist used to manage stress-related neuronal and hormonal responses.
6. **JZP150:** Experimental small molecule formulated to selectively inhibit the fatty acid amide hydrolase enzyme (FAAH)
7. **Lu AG06466:** Highly selective inhibitor of monoacylglycerol lipase (MAGL), the main enzyme responsible for the breakdown of the endocannabinoid ligand 2-arachidonoylglycerol (2-AG).

8. **NBTX-001:** Medical gas composed of 30 xenon, 30% oxygen, and 40% nitrogen. NMDA, AMPA, nACh, 5-HT3 receptor antagonist. Reduces pro-inflammatory cytokines and increases cell survival factors as well as growth factors.
9. **NYX-783:** Positive allosteric modulator of NMDA receptors synthesized using a novel chemical approach from a hypervariable region of a single monoclonal antibody with NMDA receptor modulating properties.
10. **SRX246:** Vasopressin receptor antagonist (V1aR), a neuropeptide that modulates physiological and emotional responses to the threat.
11. **TNX-102 SL:** Alpha 1 adrenergic receptor antagonists. Histamine H1 receptor antagonists; Serotonin 2A receptor antagonists.
12. **TTI-0102:** New chemical entity, cysteamine precursor.

Since last year, the molecule PRAX-114 is no longer in development for the PTSD indication whereas Balovaptan has emerged as a molecule to consider in PTSD.

Among the 12 new molecules, NYX-783 and NBTX-001 are the molecules considered to be closest to FENM action mode. NBTX-001 must be used in a specific structure (home administration is not possible), suggesting that NYX-783 is the most relevant competition for ReST FENM.

5. Biomarkers under PTSD

According to several studies, post-traumatic stress can be a systemic disease, affecting not only the brain, but the entire body. Therefore, disease signals likely span several biological domains, including genes, proteins, cells, tissues, and physiological changes in the body. The identification of these signals could help in diagnosis, and therapeutic decision-making complementary to those already existing.

For example, avoidance symptoms in veterans with PTSD may be related to arginine vasopressin (AVP) levels and, as such, may serve as a biomarker for increased aggression in men with PTSD. Hence the interest of using an antagonistic treatment of AVP (SRX246, Azevan). More recently, studies supporting a role for inflammation-driven leakiness of the blood-brain and gut barriers in emotion regulation and mood are highlighted. Stress-induced exacerbated inflammation fragilizes these barriers which become hyperpermeable through loss of integrity and altered biology. This could lead to representative treatments and specific biomarkers improving our understanding and way of treating current, and also future mood and anxiety patients.

The use of magnetic resonance imaging (MRI) would also uncover potential brain biomarkers of PTSD in people with traumatic brain injury. Differences in volume in brain regions were found that would predict PTSD at 3 months. Although the biomarker of brain volume differences is not yet sufficiently substantiated to provide clinical indications, it paves the way for possible scientific advances in the diagnosis of PTSD.

Biomarkers are to be considered in diagnosis and therapeutic decision-making complementary of PTSD management.

Conclusion

The objective of this report was to draw a mapping on scientific and business data on the management of PTSD.

PTSD is a public health problem; it affects about 15.4 million adults evenly distributed between Europe and U.S. In a recent survey the total annual economic burden for US society for PTSD reaches to $232 billion, including $76.1 billion in medical cost and $46.2 billion in unemployment for the civil population. The part of the economic burden concerning veterans reaches $42.7 billion.

The number of clinical studies conducted on PTSD is increasing, they amounted to 4% of psychiatric trials in 2001 whereas they represent 7% of psychiatric trials in 2020, showing a growing interest in this complex pathology certainly due to lack of real effective treatment.

It appears that clinical studies are mostly (70%) conducted in the United States and on the civilian population (71%). Interestingly and not surprising, 98% of veteran's studies are sponsored by the United States.

On the 359 clinical trials registered, the main intervention studied is behavioral, matching the current management of PTSD mainly oriented towards psychotherapies (*or psychotherapy associated to drug treatment*). This could also be related to the fact that no efficient pharmaceutical treatment is currently available even if two molecules (Sertraline and Paroxetine, dating from the 90's) are authorized for the management of depression associated with PTSD.

Only 5% of sponsors of clinical studies are industrial, conducting mostly clinical studies on drugs (74%). Among these industrial players, we identity 3 start-ups closed (mainly due to lack of funding or insufficient efficacy of the molecule), 4 start-ups acquired by a major pharma and 2 companies in partnership with a major pharma. 7 start-ups, 2 biotechs and 3 major company are identified as active in the clinical development of a new molecule (12 new molecules in development) and 1 major company in the clinical development of a biomarker (1 biomarker in development)

Among clinical studies conducted with a drug (20%), more than 120 molecules were or are currently evaluated.

Regarding repositioning molecules, Brexpiprazole (in combination with Sertraline) is the molecule considered to have the highest potential to obtain a market authorization in the management of PTSD within a short period of time. Results of a phase III study showed a decrease in PTSD symptoms (CAPS-5) during Brexpiprazole/Sertraline administration.

We identified 12 new molecules to be considered and more than 50 repurposing or repositioning molecules. NYX-783 and NBTX-001 are the two new molecules considered to be closest to FENM action mode. NBTX-001 must be used in a specific structure (home administration is not possible), suggesting that NYX-783 is the most serious concurrent on FENM. Interestingly, the mode of action of NYX 783, by activation of declining NMDA function in neurons expressing the 2B subtype is in full contrast with FENM (which does not target NMDA 2A and 2B at physiological doses) positions the molecule in the framework of established long-going PTSD, while FENM mode of action allows to target earlier PTSD situation as well.

Appendix 1: Information on the distribution of clinical trials

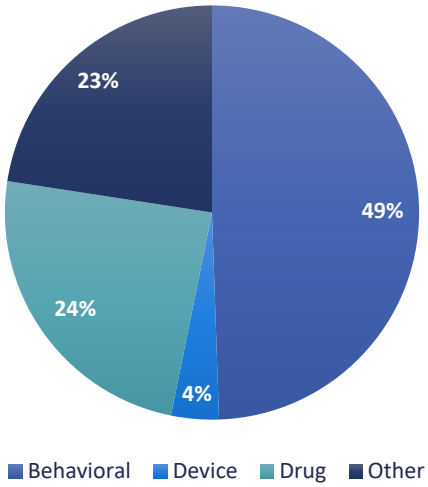


Figure 16: Clinical trials registered on PTSD before 2015 Ranking (%) by type of intervention

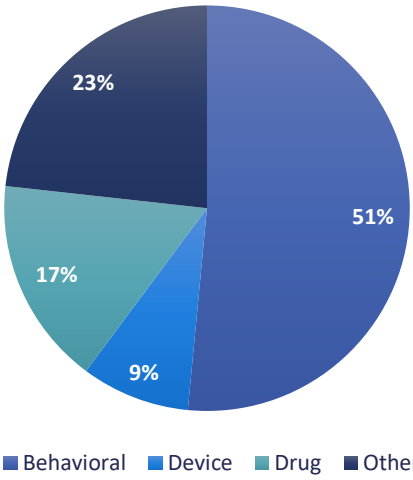
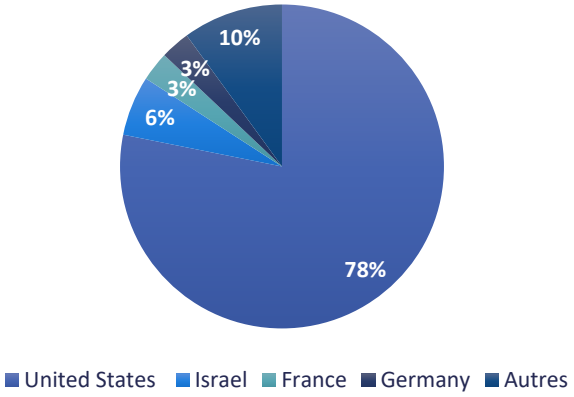
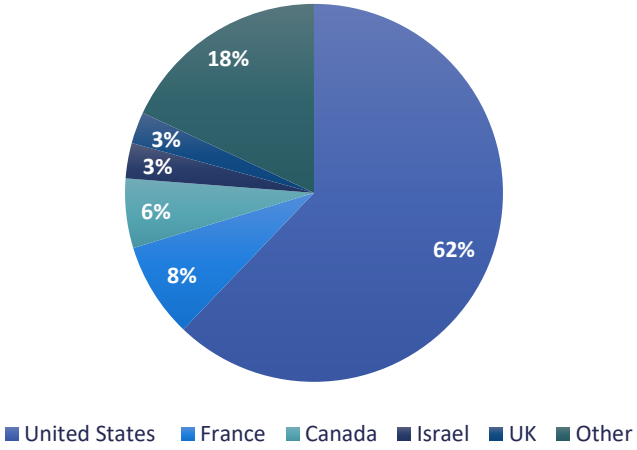


Figure 17: Clinical trials registered on PTSD after 2015 Ranking (%) by type of intervention





Country	Number of clinical trials	%
United States	640	77
Israel	49	6
Germany	24	3
France	24	3
Canada	14	1
Other	82	10
Total	**833**	**100**

Figure 18: Location of Clinical Trials - Before 2015

Country	Number of clinical trials	%
United States	596	62
France	78	8
Canada	57	6
Israel	29	3
UK	26	3
Other	223	18
Total	**959**	**100**

Figure 19: Location of clinical trials – After 2015

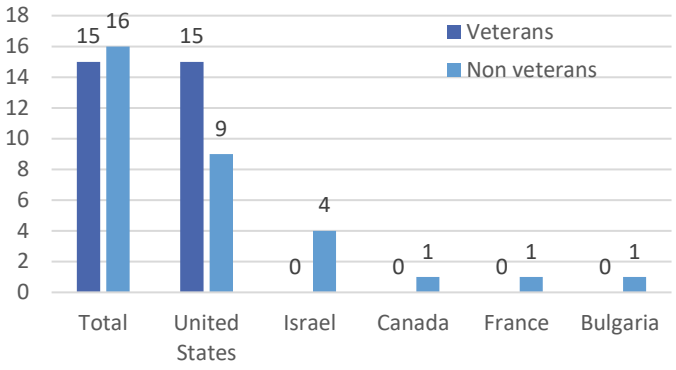


Figure 20: Localization of clinical trials on PTSD "device" - Before 2015

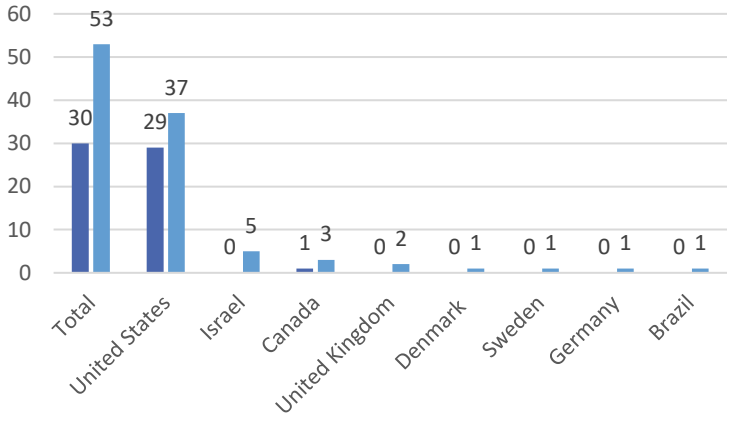


Figure 21 : localization of clinical trials on PTSD « device » - After 2015

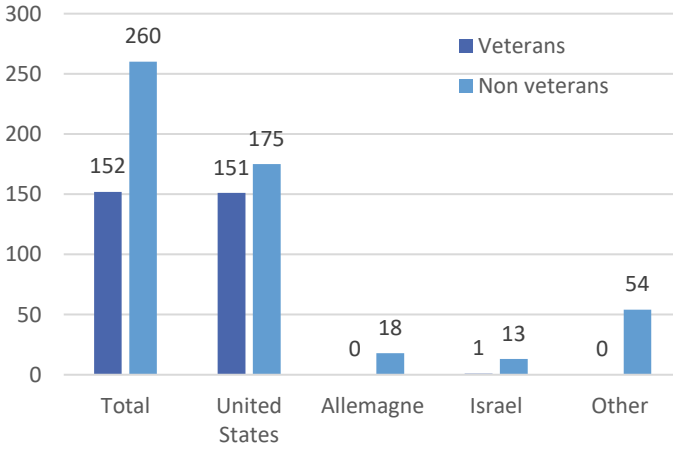


Figure 22: Localization of clinical trials on PTSD "behavorial" - Before 2015

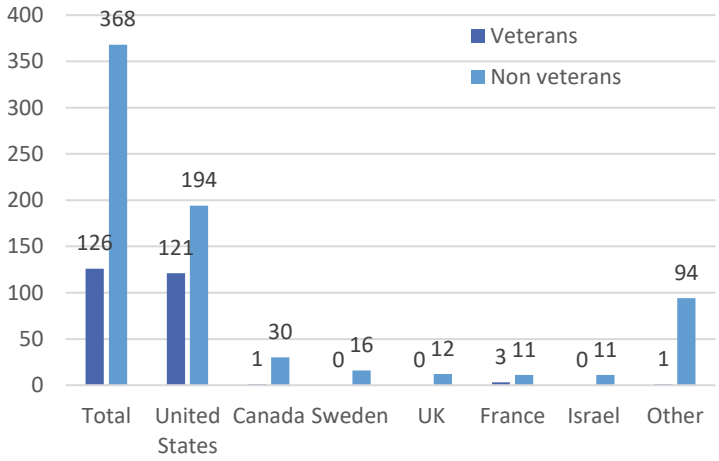


Figure 23: Localization of clinical trials on PTSD "behavorial» – After 2015

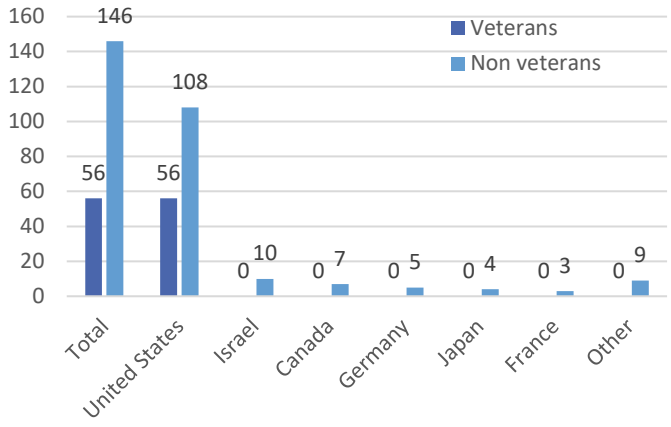


Figure 24 : localization of clinical trials on PTSD « drugs » - Before 2015

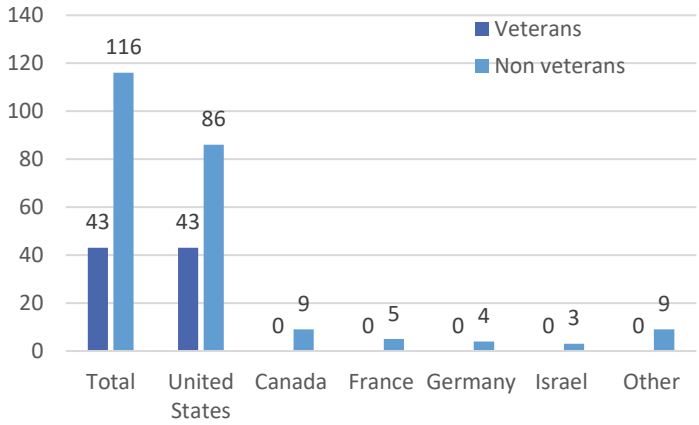


Figure 25: Localization of clinical trials on PTSD "drugs" – After 2015

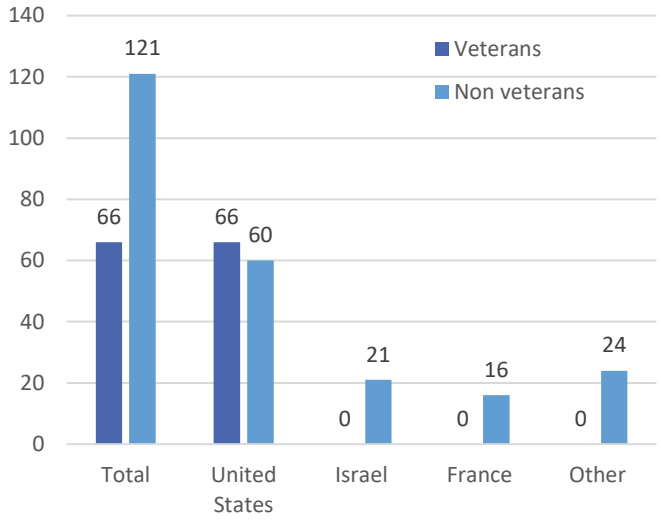


Figure 26 : localization clinical trials on PTSD « other » - Before 2015

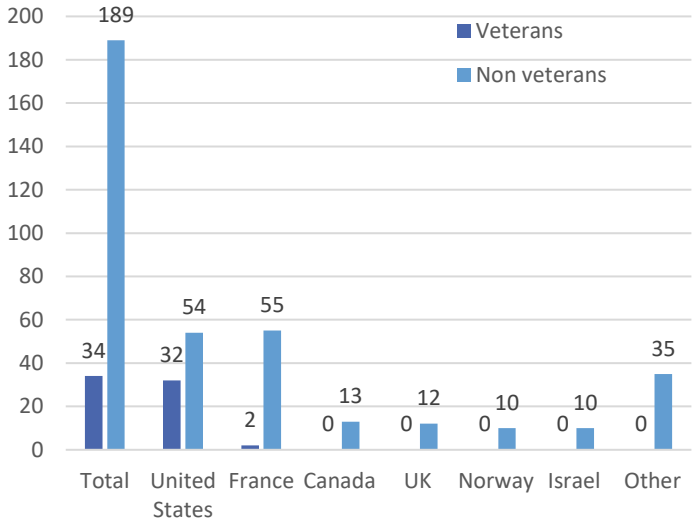


Figure 27: Localization clinical trials on PTSD "other" – After 2015

Appendix 2: List of molecules identified in clinical trials

- Aleozen: dietary supplement, plant extracts that helps treat states of stress, insomnia, and anxiety.
- Alloprégnanolone (THP, Brexanolone): hormone present in the blood and brain. It comes from the metabolism of progesterone. Has anxiolytic effects at the central level. This effect is due to the attachment of the hormone to the GABA-A receptors. Therefore, it is also associated with anticonvulsant, hypnotic, sedative, analgesic and anesthetic effects. A deficiency of this hormone is correlated with an increased risk of depression, as well as mood disorders. The biosynthesis of Allopregnanolone begins with the conversion of progesterone to 5α-dihydroprogestby5α-reductase type I. Then, the isoenzymes 3α-hydroxystéroïde oxydoréductase convert the intermediate compound into Allopregnanolone. Depression and anxiety are common side effects of 5α-reductase inhibitors such as finasteride and dutastewrinkle. This is thought to be caused in part by inhibition of Allopregnanolone synthesis. The latter seems to have some effectiveness in treating postpartum depression. Allopregnanolone would also facilitate neurogenesis that reversed cognitive deficits in a mouse model of Alzheimer's disease. The epimer-5β of this compound (pregnanolone; 3α-hydroxy-5β-pregnan-20-one) has properties close to Allopregnanolone. Its 3β-methyl analogue, Ganaxolone is being developed for the treatment of epilepsy. FDA approval in March 2019 of the first drug against depression in new mothers, Brexanolone (Zulresso brand, Sage Therapeutics laboratory). Brexanolone is a synthetic form of Allopregnanolone. This new drug works very quickly, in two days, while traditional antidepressants can take weeks or months to take effect.
- ALTO-100: Nonsteroidal anti-inflammatory drugs (NSAIDs). It is used for the short-term relief of pain, and inflammation in the joints and muscles. It works by inhibiting cyclooxygenase (COX 1 and 2) an enzyme found in the brain. It can help relieve pain found in rheumatoid arthritis and osteoarthritis.
- Aprépitant: antiemetic, powerful anti-nausea belonging to the family of neurokinin receptor antagonists. It blocks receptors in an area of the brain that controls nausea and vomiting. Used to prevent nausea and vomiting caused by cancer chemotherapy.
- Aripiprazole: antipsychotic, indicated for the treatment of schizophrenia as well as for the treatment of acute mania and mixed episodes associated with bipolar disorder. Commercialized under the name of Abilify.
- Asenapine: an atypical antipsychotic used to treat schizophrenia and acute mania associated with bipolar disorder. It was chemically derived by modifying the chemical structure of the tetracyclic antidepressant, Mianserin. Commercialized among others under the brand name Saphris.
- Atomoxetine: a potent and highly selective inhibitor of the pre-synaptic transporter of noradrenaline. Used to treat attention deficit disorder with or without hyperactivity.
- Atorvastatin: lipid-lowering agent of the statin family. It lowers the levels of cholesterol and triglycerides circulating in the blood. Studies have also shown the ability of atorvastatin to reduce the risk of mortality and cardiovascular events (myocardial infarction, stroke). Used in addition to a suitable diet in the treatment of excess cholesterol associated or not with an excess of triglycerides, when the diet and other non-drug measures (physical exercise, weight loss) have proved insufficient. Also used in the prevention of stroke in high-risk patients.
- Balovaptan: selective small molecule antagonist of the vasopressin V1A receptor which is under development by Roche for the treatment of autism. As of August 2019, it is in a phase III clinical trial for adults and a phase II clinical trial for children for this indication. On 29 January 2018, Roche announced that the FDA had granted Breakthrough Therapy Designation for Balovaptan in individuals with autism spectrum disorder (ASD). The FDA granted this based on the results of the adult phase II clinical trial called VANILLA (Vasopressin ANtagonist to Improve sociaL communication in Autism) study.
- BI 1358894: Inhibitor of trpc4 and TRPC5 cationic channels that are widely expressed throughout the brain, with particularly high transcription levels in the cortex and amygdala.

- BNC210: Negative allosteric modulator of the nicotinic alpha 7 receptor of acetylcholine.
- Brexpiprazole (REXULTI[MC]): a new molecule (i.e., neither a metabolite nor an isomer) discovered by Otsuka and developed jointly with Lundbeck. Notice of Compliance in 2017 in Canada for the treatment of schizophrenia in adults. Unknown mode of action. However, the efficacity could involve the combination of partial agonist activity on the serotonin 5-HT1A receptor and the dopamine D2 receptor and antagonistic activity on the serotonin 5-HT2A receptor. Has been evaluated in more than 2700 people with schizophrenia in Phase II and III clinical trials, and its approval has been supported by three Phase III clinical studies. Efficacy and safety were established in two 6-week, fixed-dose, placebo-controlled, randomized phase III clinical trials and one 52-week randomized withdrawal trial in subjects with schizophrenia who had an acute exacerbation of psychotic symptoms.
- Bupivacaine (Marcaïne): strongest local anesthesic currently in use. Reserved for hospital use, it is indicated in spinal anesthesia, epidural anesthesia and certain peripheral blocks.
- Buprenorphine (Buprenex): morphine agonist-antagonist and binds to the brain receptors μ and κ. Its activity in opioid substitution therapy is attributed to its slowly reversible binding to μ receptors that would prolong the need for narcotics by drug addicts. Substance close to morphine. In heroin or other opiate addicts, it helps to suppress the withdrawal symptoms that occur during drug deprivation, and which are largely at the origin of addiction. Used, alone or in combination with naloxone, in the management of opioid addictions.
- Bupropion: antidepressant but is not used for its antidepressant properties. It decreases the symptoms of smoking cessation, without its mechanism of action in this indication being precisely known. It increases the effect of norepinephrine and dopamine on the transmission of nerve impulses between neurons.
- BX-1: (Dronabinol) CB1 cannabinoid receptor agonists; CB2 cannabinoid receptor agonists.
- [C-11] MENET: Positron emission tomography (PET) to measure stress-induced changes in norepinephrine transporter (NET) expression.
- [11C] MK-3168: Positron emission tomography (PET) tracer for fatty acid amide hydrolase, an enzyme whose activity is linked to the awakening and extinction of aversive memories, two key characteristics of PTSD.
- Carvedilol: beta-blocker with alpha-blocking properties, used in the treatment of heart failure.
- Cannabidiol (CBD): a molecule belonging to the cannabinoid family. Like THC, it is an active substance present in the hemp plant. Due to its anxiolytic properties, CBD tends to regulate the mood of consumers and to act on anxiety attacks, anxiety symptoms and all manifestations related, directly or indirectly, to depression. It differs from THC for its health benefits and its use in a medical setting in some countries.
- Clonazépam: class of 1-4 benzodiazepines, has a pharmacodynamic activity qualitatively similar to that of the other compounds of this class: muscle relaxant, anxiolytic, sedative, hypnotic, anticonvulsant, amnesiac. Specific agonist action on a central receptor that is part of the "GABA-OMEGA macromolecular receptors" complex, also called BZ1 and BZ2 and modulates the opening of the chlorine channel. Used in epilepsies and Lennox-Gastaut syndromes.
- Clonidine: antihypertensive drug of central action. It acts directly on the nerve centers that are involved in the regulation of blood pressure. Used in the treatment of high blood pressure. Sold under the brand name Catapressan.
- CORT108297: Selective glucocorticoid receptor antagonist.
- (D)-Cycloserine (or Seromycin): antibiotic extracted from *Streptomyces orchidaceus*. Active against enterococci, Nocardia, Chlamydiae and also against tuberculous bacillus.
- Desvenlafaxine: antidepressant inhibitor of serotonin-norepinephrine reuptake. Developed by the Wyeth laboratory and is marketed as Pristiq. Desvenlafaxine is one of the metabolites of venlafaxine.
- Dexamethasone: synthetic glucocorticoid hormone. Physiological glucocorticoids (cortisone and hydrocortisone) are essential metabolic hormones. Synthetic corticosteroids, including dexamethasone, are

used primarily for their anti-inflammatory effect. In high doses, they decrease the immune response. Their metabolic effect and sodium retention is less than that of hydrocortisone. It has an anti-inflammatory and immunosuppressive effect.

- Dexmedetomidine: a sedative drug α_2-agonist used in human and veterinary anesthesiology.
- DHEA: hormone of the steroid hormone family, such as sex hormones (estrogen, progesterone, androgens). It is manufactured in large quantities by the adrenal glands, it is used for the synthesis of sex hormones, testosterone and estrogen. Pis used as an adjuvant treatment for lupus erythematosus, a disease where the immune system attacks certain cells in the body. There is insufficient evidence of effectiveness of DHEA in treating age-related effects and advises against its use in view of potential adverse effects. The function of DHEA in adults is not well known. It has long been known that its production decreases with age, which suggested that it may play a role in aging. Recently, has been administered to volunteer subjects to evaluate the effects. This study showed that DHEA could improve skin condition, libido and slow bone loss only in women over the age of 70. No benefit was found in younger women or men of any age. Is not considered a medicine and is over the counter in some countries. There is no control over the product offered for sale.
- Diazepam: specific agonist action on a central receptor that is part of the complex "GABA-OMEGA macromolecular receptors", also called BZ1 and BZ2 and modulating the opening of the chlorine channel. Indicated in the management of anxieties, anxiety attacks, febrile convulsions in children, delirium, epileptic states of evil, inductions of general anesthesia, premedication of endoscopy, alcoholic withdrawals, tetanus.
- Divalproex (Divalproate): mood regulator (thymoregulator). It also has anticonvulsant properties. Used in the treatment of manic phases in adults with bipolar disorder, in case of contraindication or intolerance to lithium.
- Dobutamine: Aninotropic gent whose primary activity results from stimulation of cardiac adrenergic receptors. Unlike that of dopamine, the action of dobutamine is not related to the endogenous release of norepinephrine and therefore does not depend on the cardiac reserves of this mediator. In humans, dobutamine increases ejection volume and cardiac output while it decreases filling pressures as well as systemic and pulmonary vascular resistance. It does not act on dopaminergic receptors. Because of this, it does not selectively dilate the renal or splanchnic vessels. It can, however, improve renal blood flow, glomerular filtration rate, urine flow and sodium excretion, by increasing cardiac output and causing non-selective vasodilation. Management of low cardiac outputs and cardiovascular functional explorations. Administered as a continuous infusion for its positive inotropic properties, especially in cases of severe heart failure.
- Doxazosin: antihypertensive, more precisely alpha-1-blocker. Used in the treatment of slightly to moderately high blood pressure, urinary disorders in cases benign prostatic hypertrophy.
- D-serine: one of the most abundant amino acids in proteins. D-Serine, synthesized by serine racemase from L-serine, serves as a neural signal by activating the NMDA receptor in the brain. It has recently been shown that in a minimal culture medium, supplemented with dialysis serum instead of whole serum, the culture of a wide variety of human cell strains is possible, but that the regular or optimal growth of a number of these cells (HeLa, HeLa S3, conjunctival, or KB) is inhibited, apparently due to a nutritional deficiency; this deficiency can be overcome by adding the seven amino acids considered nutritionally non-essential, but in most experiments the addition of serine alone is sufficient to allow the normal growth of these cells. French scientists are currently working (March 2020) on a potential preventive treatment for Alzheimer's disease from this amino acid. A related metabolic deficit would have been identified by their team.
- Duloxetine: inhibitor of both serotonin (5-HT) and norepinephrine (NA) reuptake. It weakly inhibits dopamine reuptake and has no significant affinity for histamine, dopaminergic, cholinergic and adrenergic receptors. Dose-dependent increases extracellular levels of serotonin and norepinephrine in different areas of the brain in animals. Used for the management of neuropathic pain of diabetics, major depressive episodes, generalized anxiety disorders.

- Enbrel: a competitive inhibitor of TNF (tumor necrosis factor) binding to its surface receptors, thereby inhibiting the biological activity of TNF. Tumor necrotizing factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. High levels of TNF are also found in the synovial membranes and psoriasis plaques of patients with psoriatic arthritis, and in the serum and synovial tissue of patients with ankylosing spondylitis. The supposed mechanism of action consists of a competitive inhibition of TNF binding to TNFR on the cell surface: TNF-mediated cellular responses are blocked by making TNF biologically inactive. It could also modulate biological responses controlled by other downstream molecules (e.g., cytokines, adhesins or proteinases) whose activity is induced or regulated by TNF. Used in the treatment of rheumatoid arthritis, plaque psoriasis, ankylosing spondylitis, axial spondyloarthritis, psoriatic arthritis, juvenile idiopathic arthritis.
- Escitalopram: antidepressant selective inhibitor of serotonin reuptake. Commercialized in various countries under the names Of Lexapro, Cipralex, Sipralexa and Seroplex. Used in the treatment of depression and anxiety.
- Estradiol: sex hormone. Dnatural cholesterol metabolism (via testosterone) which is necessary for the maintenance of fertility and secondary sexual characteristics in females of mammals including women. Endogenous production of estradiol (17β-estradiol or "E2") also exists in the visual cortex of the brain, in the primary visual cortex, with receptors located in the same region, whose function is not yet understood. Synthetic 17-ß estradiol is chemically and biologically identical to human endogenous estradiol. It replaces the cessation of estrogen production in postmenopausal women and relieves climacteric symptoms of menopause. Estrogens prevent bone loss related to menopause or oophorectomy.
- Eszopiclone: hypnotic, properties close to benzodiazepines. Commercialized among others under the brand name Lunesta, treatment of insomnia.
- Fluorodeoxyglucose (18F): c radiopharmaceutical glucose analogue where the hydroxyl of carbon 2 of glucose is replaced by a radioactive fluorine atom (fluorine F18). If the same metabolic pathway as glucose, it is converted into 18FFDG6phosphate which concentrates in cells characterized by increased glucose consumption, such as tumor cells. Indicated for positron emission tomography (PET) in oncology, cardiology, neurology.
- Fluoxetine: Selective serotonin reuptake inhibitor used as an antidepressant in the treatment of severe depression, obsessive-compulsive disorder, bulimia nervosa, premenstrual dysphoric disorders, and many other conditions. Marketed under the brand name Prozac, Sarafem.
- Fluticasone Propionate: combines two substances whose mechanisms of action are different: a corticosteroid (fluticasone propionate) which has a marked anti-inflammatory activity on the mucous membranes, especially those of the bronchi and a bronchodilator (salmeterol) which fights against the abnormal contraction of the muscles of the wall of the bronchi; it is related to a natural substance, adrenaline, but, unlike this substance, it has little effect on the heart. Used in the background treatment of asthma, when the use of the combination of a corticosteroid and a bronchodilator is deemed necessary and in the symptomatic treatment of COPD.
- Ganaxolone: modulator of GABAA receptors. Includes inhibition of abnormal electrical discharges that cause seizures and status epilepticus or restoration of balance in disrupted neuronal activity in other CNS disorders. Module both synaptic and extrasynaptic GABAA receptors, could treat epileptic seizures resistant to other available molecules as well as other brain disorders.
- GSK561679 (Verucerfont): various studies between 2006 and 2010 conducted by GSK on PTSD, anxiety disorders, depressive disorders, alcohol dependence.
- Guanfacine: Like clonidine, is a derivative of imidazolines, and its mechanism of action is similar to that of clonidine. Indicated to treat hypertension. It is also used in attention deficit disorder and anxiety. Was approved by FDA in 1986 and by the European Medicines Agency in 2015.
- Haloperidol: antipsychotic neuroleptic of the butyrophenone family. It has anti-dopaminergic properties responsible for the antipsychotic effect sought in therapeutics. Indicated in psychotic agitations, psychotic

aggressiveness, anxiety, severe behavioral disorders in children in the context of autistic syndrome, psychotic states, abnormal movements, diseases of Gilles de la Tourette's tics, nausea and vomiting induced by radiotherapy.

- Hydrocortisone (cortisol): contains a hormone close to natural cortisone. Used as a replacement therapy to replace natural cortisone when it is no longer sufficiently secreted by the adrenal glands. This lack of secretion is due to the adrenal glands themselves: Addison's disease, removal of the adrenals or the insufficiency of another gland that controls adrenal secretion: disease or removal of the pituitary gland. Active on certain inflammatory processes such as contact hypersensitivity and the itchy effect related to them. Vasoconstrictor, it inhibits cell multiplication. Management of multiple pathologies (skin pathologies, adrenal insufficiency, Crohn's disease, insect bites, bacterial infections, ...)
- Ifenprodil: inhibitor of the NMDA receptor, in particular of the GluN1 and GluN2B subunits. Indicated in the management of chronic arterial disease obliterating of the lower limbs.
- Iloperidone: antipsychotic, called "atypical" antipsychotic, because it is different from older antipsychotic drugs, available since the 1950s. The way it acts is not perfectly elucidated, but it is supposed to attach to certain receptors present on the surface of nerve cells in the brain. This disrupts signals transmitted between brain cells by "neurotransmitters," chemicals that allow nerve cells to communicate with each other. Withdrawn from the market in 2013. Treatment of symptoms of schizophrenia.
- Insulin: the main activity is the regulation of carbohydrate metabolism. On the other hand, insulin has several anabolic and anticatabolic actions in different tissues. In muscle, these effects include an increase in the synthesis of glycogen, fatty acids, glycerol, proteins and an increase in amino acid fixation, as well as a decrease in glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid elimination. Biogenetic human insulin is used in the management of insulin-dependent diabetes.
- JPZ150: Inhibitor of fatty acid amide hydrolase, an enzyme whose activity is linked to the awakening and extinction of aversive memories, two key characteristics of PTSD.
- Ketamine: psychotropic drug used as a general anesthetic. Also used as an analgesic, sedative, in the treatment of chronic pain and in veterinary medicine. A particular anesthesia, called dissociative, by decreasing the activity at the level of the neocortex and the subcortical structures (thalamus) and by increasing the activity at the level of the limbic system and the reticulated substance. This anesthetic state is characterized by deep and prolonged analgesia, a loss of consciousness that results more in a disconnection of the patient than in true sleep, the preservation of pharyngeal and laryngeal reflexes, the maintenance or discreet increase in muscle tone, as well as the usual cardiovascular and respiratory stimulation. Awakening is early but it takes some time before the patient has recovered from absolutely normal behavior. It is, most often, progressive and without agitation; but in some subjects, psycho mimetic phenomena may occur at the emergence phase; awakening may be delayed if ketamine is combined with barbiturates or neuroleptics. In the United States, is marketed since March 2019 as an antidepressant under the name Spravato, nasal spray.
- Keto dehydroepiandrosterone: pro hormone produced by the metabolism of the pro hormone dehydroepiandrosterone. 7-oxo-DHEA is even more effective than DHEA in inducing heat production. It is not directly converted into testosterone or estrogen and has been studied asa potentially more useful parent of DHEA. The World Anti-Doping Agency lists it as a prohibited anabolic agent. The FDA has proposed that it be banned from use in compound drugs.
- Lanicemin: Afege-resistant NMDA receptor antagonist that was being developed by AstraZeneca for the management of severe and treatment-resistant depression. Differs from ketamine in that it is a low-trapping NMDA receptor antagonist, exhibiting fast-acting antidepressant effects similar to those of ketamine in clinical trials, but with little or no psychotomimetic side effects. However, Lanicémine did not meet the evaluation criteria of the study and its development was halted by AstraZeneca in 2013.

- Levodopa (L-DOPA): antiparkinsonian that belongs to the dopaminergic family. Levodopa converts to dopamine in the body. It aims to fill the dopamine deficiency in certain areas of the brain, characteristic of Parkinson's disease. It acts mainly on muscle rigidity and the reduction of rest tremors specific to this condition. Carbidopa stabilizes the effect of levodopa by preventing its degradation. Treatment of Parkinson's disease.
- Levetiracetam: derived from pyrrolidone (the S-enantiomer of acetamide alpha-ethyl-2-oxo-1-pyrrolidine), chemically unrelated to existing anticomitial active substances. Mechanism of action not fully elucidated but appears to be different from the mechanisms of action of existing antiepileptic drugs. Used in the treatment of epilepsy.
- Lipopolysaccharide: a major component of the outer membrane of Gram-negative bacteria. These are glycolipids comprising a lipid region called lipid A, most often made of a disaccharide of phosphorylated glucosamines and carrying fatty acids in ester or amide bond. Ivermectin is indicated for the topical treatment of inflammatory rosacea lesions in adults and belongs to the class of avermectins that have anti-inflammatory effects by inhibiting the production of inflammatory cytokines induced by lipopolysaccharide.
- Lithium: in oligotherapy, lithium, trace mineral element has an action on the nervous system. In psychiatry, lithium is a normothymic (mood regulator). In dermatology, the mechanisms of action of lithium in the treatment of seborrheic dermatitis are incompletely known. Orally, lithium is used in the management of sleep disorders, irritability, manic or hypomanic states, bipolar disorder, schizoaffective disorders. Dermal, lithium is used in the management of seborrheic dermatitis.
- Lofexidine: α-2-adrenergic receptor agonist, with a very high affinity for the α-2A subtype. The molecule inhibits the release of norepinephrine into the central and peripheral nervous systems. Indicated to alleviate withdrawal symptoms of heroin and other opiates in adults.
- Losartan: antihypertensive drug that belongs to the family of angiotensin II inhibitors. It blocks the action of angiotensin II. This substance, naturally present in the body, causes a contraction of the arteries that increases blood pressure and tires the heart. Used in the treatment of hypertension and to prevent stroke in hypertensive people with increased heart volume, kidney damage in hypertensive diabetics with proteinuria, chronic heart failure.
- Lu AG06466: Modulator of endocannabinoid neurotransmission, it inhibits the degradation of the endocannabinoid 2-arachidonoylglycerol (2-AG).
- MDMA (3,4-methylenedioxy-N-methylamphetamine): sympathomimetic amine, a psychostimulant molecule of the amphetamine class. It works by causing the brain to release more than usual certain neurotransmitters: serotonin, dopamine and norepinephrine. MDMA binds as an agonist to numerous receptors, including among others serotonin receptors ($5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, $5\text{-}HT_{2B}$, $5\text{-}HT_{2C}$), adrenergic receptors (α_1, α_{2A}, β), dopamine receptors (D_1, D_2), its main psychedelic effect being due to $5\text{-}HT_{2A}$ serotonin receptor activation. The entactogenic qualities of MDMA may be related to the indirect secretion of oxytocin via the massive activation of the serotonin system. Oxytocin is a peptide hormone released during particular moments related to affect such as birth, orgasm, social recognition or empathy. Powerful sympathomimetic and serotonergic, it is often used as a drug, then sold in the form of crystals (often impure) or pills under the name of ecstasy (variable content of active ingredient). These products often contain not only MDMA but also related molecules such as synthetic by-products (MDA or MBDB) or synthetic analogues such as Methylone. MDMA is a stimulant of the central nervous system that has particular psychotropic characteristics, qualified by some authors as entactogens It is also a powerful serotonergic, which transforms it in high doses, or in case of regular use, into a neurotoxic . It is particularly prevalent in the festive world, frequently associated with the techno movement, rave parties and electronic music. Classified as a narcotic drug in France, and listed on the 1971 Convention on Psychotropic Substances. These biological properties, rare in psychedelics, indicate this for the treatment in assisted therapy of PTSD. However, its use for therapeutic purposes was quickly discontinued following its prohibition and was then taken up in the early 2000s but also experimental protocols in Switzerland and Spain

in the treatment of PTSD and other applications in psychiatry. According to some authors, MDMA may be useful in the treatment of PTSD. Currently, no drugs containing MDMA are authorized and/or marketed.

- Memantine: blocks glutamate receptors, a neurotransmitter involved in the occurrence and progression of certain symptoms of Alzheimer's disease. It thus makes it possible to modulate the transmission of messages between nerve cells that have a role in the memory process. Treatment of moderate to severe forms of Alzheimer's disease.
- Pomaglumetade methionine amide: an amino acid analogue that acts asa highly selective agonist for the mGluR2 and mGluR3 subtypes of group II metabotropic glutamate receptors. Research has focused on potential antipsychotic and anxiolytic effects. It is intended for the treatment of schizophrenia and other anxiety and psychological disorders by modulating glutamatergic activity and reducing the presynaptic release of glutamate in the synapses of the limbi ques areas and the forebrain related to these disorders. Studies have focused on LY-2140023, as it has better oral absorption and bioavailability. Eli Lilly stopped development in 2012 after a phase 3 failure, confirmed in 2013 during a study that did not show any benefit on the symptoms of schizophrenia. In 2015, Denovo Biopharma identified "a subset of patients who showed significantly improved results".
- Blue methylene (methylthioninium chloride): at low concentrations, accelerates the conversion of methemoglobin to hemoglobin. Colored tissues selectively. By injectable route, it is used in the management of methemoglobinemias. Ophthalmically, it is antiseptic and is used in the management of non-infectious conjunctival irritations.
- Methylphenidate: stimulant of the central nervous system. The relationship between mode of action and therapeutic effect in attention deficit hyperactivity disorder (ADHD) is not known. It would block the reuptake of norepinephrine and dopamine at the level of presynaptic neurons and increase the release of these monoamines into the extraneuronal space. It is currently the only treatment available for children with a Truble Deffect At ttention/Hyperactivity. It is also used in the treatment of narcolepsy. Ritalin®, Concerta®, Quasym®, Medikinet®.
- Mianserin: antidepressant, also has a tranquilizing and sedative effect. Used in the treatment of depressive states.
- Midazolam: sedative hypnotic derived from the group of imidazobenzodiazepines. Has intense sedative and hypnotic action. It also carries out anxiolytic, anticonvulsant and muscle relaxant activities. After IV or IM administration, short-term anterograde amnesia appears (the patient no longer remembers the events that occurred during the maximum activity of the product); used in the management of anesthesia and sedation. Orally, used in the management of seizures in children and infants.
- Mifepristone: synthetic steroid with anti-progestogen action by competition with progesterone at its receptors. Used in the management of therapeutic terminations of pregnancy.
- Minocycline: antibiotic of the cyclin group. It is part of the second generation tetracyclines. It is indicated against many bacterial infections. It is mainly used as an anti-acne.
- Mirtazapine: antidepressant with sedative effect. Treatment of depressive states.
- Modafinil: powerful psychostimulant. It helps to improve the alertness of patients suffering from narcolepsy. Its mechanism of action is poorly understood. Used in adults in the treatment of excessive drowsiness during the day when combined with narcolepsy.
- Nabilone: narcotic used to treat severe nausea and vomiting. It is part of the cannabinoids, analogous to dronabinol. Also used to increase appetite. It is marketed under the name Césamet in the United Kingdom, Canada and Spain where it is prescribed for the relief of chronic pain or as a hypnotic.
- N-acetylcysteine: in pulmonology, mucomodifier of the mucolytic type. It exerts his action on the freezing phase of mucus, probably by breaking the disulfide bridges of glycoproteins, and thus promotes sputum. Used in the management of disorders of bronchial secretions and in the management of bronchial congestion in the

tracheotomis. In ophthalmology, collagenase inhibitor, proteolytic enzyme secreted in significant quantities during any damage to the epithelium and causing the degradation of corneal collagen polypeptide fibers; used in the management of corneal healing. In toxicology, acetylcysteine is a precursor to glutathione, which can enter cells. It is essentially through this way that it protects hepatocytes. Glutathione neutralizes, in fact, the electrophilic entities produced by the metabolism of paracetamol. By injectable route, it is used in the management of acute paracetamol poisoning. In combination with benzalkonium and tuaminoheptane, it is used in the management of nasopharyngitis.

- Nabiximols (Sativex): treatment of multiple sclerosis to reduce neuropathic pain, spasticity, overactive bladder, and other symptoms. The active compounds in this product are THC and CBD, compounds produced by the Cannabis sativa plant. It is different from other cannabinoids used in medicine because it consists of a mixture of compounds extracted directly from the cannabis plant and not a single synthetic molecule. A provisional MA of 6 months was granted by the ANSM. Initially, only neurologists and hospital rehabilitation doctors will be allowed to prescribe it. Pharmacies will have to store it in a safe, as required by law for health products derived from narcotics. Nevertheless, in 2018, the drug has still not been marketed in France, due to a lack of agreement on its price.
- Nepicastat: inhibitor of dopamine beta-hydroxylase, an enzyme that catalyzes the conversion of dopamine into norepinephrine. It has been studied as a possible treatment for congestive heart failure and appears to be well tolerated as such. Studied in the PTSD.
- Neuropeptide Y: consisting of 36 amino acids, has an orexigen effect. It is present in the central nervous system and the autonomic nervous system (sympathetic fibers where its distribution follows that of norepinephrine). Its release in the hypothalamus is increased during fasting, inhibited by leptin and insulin and increased by glucocorticoids. The most notable effect of NPY is the stimulation of appetite by hypothalamic effect. It also decreases the thermogenesis of adipocytes and promotes obesity. It also has an anxiolytic and sedative effect, an antinociceptive (analgesic) effect. It could play a role in the central regulation of blood pressure, because, injected into certain areas of the animal's brain, it causes hypotension and bradycardia. It could inhibit the release of certain mediators, that of glutamate for example. It would promote the secretion of ACTH and inhibit that of GH and TSH.
- Nicotine: a toxic alkaloid derived mainly from the tobacco plant (Nicotiana tabacum) used as a psychotropic (stimulant), particularly when inhaling tobacco smoke. This molecule is partly responsible for smoking dependence. Nicotine acts directly on the nervous system, triggering addiction in homme.
- Nitrous oxide 'nitrous oxide'): a colourless gas, almost odourless, oxidizing and heavier than air. It acts as a central nervous system depressant, with a dose-dependent effect. Its low anesthetic power (due to its low solubility in blood and oil) explains why, for anesthesia, it must be used in combination with other volatile anesthetics or administered intravenously. Its analgesic power is observed at low doses (low concentration). It works by increasing the pain threshold. It is a depressant of the synaptic transmission of nociceptive messages and activates the sympathetic nervous system whose noradrenergic neurons play a role in nociception. Has a weak amnesic effect and provides very low muscle relaxation. Used in general anesthetics and analgesics.
- NYX-783: Positive allosteric modulator of NMDA receptors currently in Phase 2 development for the treatment of PTSD (Aptinyx).
- Oxytocin (Syntocinon): octopeptide synthesized in the hypothalamus that stimulates milk emission and uterine contractions. Hormone that behaves in the brain like a neuropeptide. Increases the frequency and intensity of uterine contractions. Used in the management of postpartum hemorrhagic uterine atonias, inductions of uterine retraction after obstetric surgery, insufficiency of uterine contractions during labor.
- Omega 3: essential fatty acids. They can be transformed, via cyclooxygenase and lipoxygenase into different molecules serving as signaling agents such as prostaglandins, thromboxanes or leukotrienes. Other compounds produced have an anti-inflammatory and anti-thrombotic role. They can also act directly at the cellular level

without undergoing transformation: they act on certain ion channels, which could reduce the risk of heart rhythm disorders. The absorption of omega-3 contributes to normal cholesterol levels. At the same time, omega-3s decrease blood triglycerides. They seem to slightly decrease the level of blood pressure as well as the heart rate. They also decrease platelet aggregability.

- Orvepitant: neurokinin receptor antagonist 1. Phase 2 study on PTSD, anxiety and depressive disorders abandoned.
- Paliperidone: selective agent blocking the effects of monoamines, whose pharmacological properties are different from those of conventional neuroleptics. It binds strongly to serotonergic 5-HT2 and dopaminergic D2 receptors. Also blocks alpha 1-adrenergic receptors and, to a lesser degree, histaminergic H1 and alpha 2-adrenergic receptors. Does not bind to cholinergic receptors. Although it is a potent D2 antagonist, which is believed to be responsible for the beneficial effect on positive symptoms of schizophrenia, it results in less catalepsy and decreases motor skills less than conventional neuroleptics. Management of schizophrenia.
- Paroxetine: a powerful and selective inhibitor of the reuptake of 5-hydroxytryptamine (5-HT, serotonin). Its antidepressant action and effectiveness in the treatment of obsessive-compulsive disorder, social anxiety/social phobia disorder, generalized anxiety disorder, PTSD and panic disorder appear to be due to its specific inhibition of serotonin reuptake in brain neurons. Is not chemically related to tricyclic, tetracyclic and other antidepressants available. Unlike most tricyclic antidepressants, paroxetine has little affinity for alpha 1, alpha 2 and beta adrenergic, dopaminergic (D2), 5-HT1, 5-HT2 and histaminergic (H1) receptors. This lack of interaction with post-synaptic receptors in vitro is corroborated by in vivo studies that demonstrate the absence of a depressant effect on the central nervous system as well as hypotensive properties. Authorized FDA in 1992 by the GSK group under the brand-name Paxil, Deroxat or Seroxat.
- PF-04457845: a potent and highly selective inhibitor of FAAH, and analgesic and anti-inflammatory effects in animal studies comparable to Naproxen. Has been shown to be ineffective in phase 2 clinical trials to treat osteoarthritis. Since 2021, several studies show that it could reduce the symptoms of cannabis withdrawal and cannabis use.
- Pramipexole: antiparkinsonian of the dopaminergic family. It compensates for dopamine deficiency, characteristic of Parkinson's disease, by stimulating dopamine receptors. Also used in the treatment of restless legs syndrome, when it is accompanied by troublesome disorders (insomnia, impact on daily life).
- Prazosine: chemical derivative of quinazoline, the first product of a new series of antihypertensive drugs. Determines a reduction in total peripheral resistances but the exact mechanism of action is not yet fully known. Used in hypertension, benign prostatic hypertrophy, congestive left ventricular failure, Raynaud's syndrome.
- Prednisone: Physiological glucocorticoids (cortisone and hydrocortisone) are essential metabolic hormones. Synthetic corticosteroids, including prednisone, are used primarily for their anti-inflammatory effect. In high doses, they decrease the immune response. Their metabolic effect and sodium retention is less than that of hydrocortisone. Management of a multitude of pathologies including asthma, COPD, cancer, Crohn's, lupus, hepatitis, nausea and vomiting, cerebral edema, pneumonitis, polyarthritis, rhinitis, tuberculosis, ...
- Pregabalin: an antiepileptic drug chemically related to a substance found in the brain, gamma-amino-butyric acid (GABA). Used in the treatment of neuropathic pain, epilepsy and generalized anxiety disorder.
- Pregnenolone: hormone naturally present in our body, especially in the brain. It serves as a chemical precursor for the manufacture of other hormones: DHEA, progesterone, cortisol and aldosterone. If DHEA is considered the "mother" hormone of sex hormones, pregnenolone would be the "grandmother" hormone. In some people, blood levels of this hormone decrease with age. Treatment of age-related memory disorders, to relieve depression, but also as an anti-inflammatory in the treatment of pain related to rheumatism. It is also thought to relieve menopause-related disorders such as hot flashes, vaginal dryness, urinary incontinence, mood disorders.

- Pimavanserin (Nuplazid): Agonist specific to serotonergic receptors type 5HT-2a1, with little effect on 5HT-2c. Antipsychotic approved by the FDA for the treatment of hallucinations and delusions associated with the psychosis of Parkinson's disease. Delivered by ACADIA Pharmaceuticals Inc. In schizophrenia, its action seems synergistic with risperidone but not with haloperidol.
- Progesterone: steroid hormone mainly secreted by the cells of the corpus luteum of the ovaries and the placenta. It is involved in the pregnancy and embryogenesis of many mammal species, as well as in the menstrual cycle. Synthetic progesterone is comparable to that of natural progesterone, especially gestagen, antiestrogen, weakly antiandrogen, antialdosteron. Used for the management of premenstrual syndromes, menstrual irregularities, benign mastopathies, premenopausal, menopausal replacement therapy.
- Propranolol (alvocardyl): blockers that act by blocking the action of adrenaline (and other related hormones) on many organs, including the heart, vessels and bronchi. Used in the treatment of hypertension, prevention of attacks of exertional angina, treatment of myocardial infarction, heart rhythm disorders, obstructive cardiomyopathies, certain tremors, background treatment of migraines and frontal vascular algia, prevention of heart palpitations and during stressful situations, digestive hemorrhages in patients with cirrhosis of the liver, cardiovascular manifestations of excess thyroid hormones. FDA approved in 1965 under the brand name Inderal by the AstraZeneca group.
- PRX-03140: A partial 5-HT4 receptor agonist developed by Epix Pharmaceutical for the treatment of Alzheimer's disease.
- Psilocybin: indole alkaloid with a phosphoric acid radical which is the active ingredient in some hallucinogenic mushrooms. Psilocin, a metabolized form of psilocybin, mainly interacts with the serotonergic receptor subtypes 5-HT1A, 5-HT2A and 5-HT2C: it is a mixed agonist of these receptors. Psilocybin used in a controlled manner at low doses has proven to be an excellent treatment for patients with OCD (obsessive-compulsive disorder). Effective treatment for cluster headache, extreme headache that is resistant to almost all current treatments. In depressed patients with terminal cancer, controlled use induces a decrease in anxiety, a better acceptance of the fear of death as well as an improvement in mood, a decrease or even a suppression of depression. It has also been successfully used for the treatment of incurable severe depression. In 2018 the FDA granted breakthrough potential treatment designation for psilocybin-assisted therapy for treatment-resistant depression, in 2019 for major depressive disorder. Other data, however, seem to show that it does no better than Escitalopram as an antidepressant. This molecule could also be useful in some treatments for alcoholism. It has the formation of dendritic spines and thus stimulates the neural connections. These results could explain the benefits seen in depressed people, in whom synaptic atrophy in the prefrontal cortex could be observed.
- PT-150: Glucocorticoid receptor antagonist causing deregulation of HPA axis activation.
- Quetiapine (Seroquel): neuroleptic called atypical. Some of its adverse effects are less pronounced than those of conventional neuroleptics. It has antipsychotic properties and also acts as a mood regulator (thymoregulator) and antidepressant. Used in the treatment of schizophrenia, bipolar disorder and depressive states in addition to an antidepressant. Antagonalist of both serotonergic 5-HT2A and dopaminergic D2 receptors. Authorized by the FDA in 1997. Sold by the AstraZeneca Group under the brand name Seroquel.
- Ramelteon: a sleeping pill that selectively binds to MT 1 and MT2 receptors in the suprachiasmatic nucleus (SCN), instead of binding to GABA A receptors that are associated with anxiolytic, muscle relaxant and amnesic effects. Seems to speed up the onset of sleep and change the total amount of sleep a person gets. Approved FDA for long-term use. The duration of action is much longer than that of melatonin. Sold among others under the brand name Rozerem.
- Rapamycin (Sirolimus): a molecule known for several decades; it is extracted from an algae harvested on the island of Passover. Its antimycotic, bactericidal, immunosuppressive and antiproliferative properties quickly aroused the interest of scientists. Iselective mmunosuppressor, inhibits the activation of T cells induced by

most stimuli by blocking the transduction of intracellular signals, both dependent and independent of calcium. Its effects are mediated by a different mechanism than ciclosporin, tacrolimus and other immunosuppressive agents. Experimental data suggest that sirolimus binds to the specific cytosolic protein FKPB-12 and that the FKPB 12-sirolimus complex inhibits activation of the mammalian target *of rapamycin* (mTOR), which is an essential kinase for cell cycle progression. Inhibition of mTOR results in the blocking of several specific signal transduction pathways. The net result is inhibition of lymphocyte activation, causing immunosuppression. Management of transplant rejection.

- Riluzole: agit on the central nervous system, its mode of action is not clearly elucidated. It seems to be able to slow down the destruction of nerve cells (motor neurons), responsible for amyotrophic lateral sclerosis (or Charcot's disease). This glutamanergic modulator inhibits the release of glutamate and improves AMPA trafficking and excessive synaptic glutamate clearance, resulting in neuroprotective properties. Indicated in the treatment of amyotrophic lateral sclerosis to improve life expectancy or to delay the moment when artificial respiration becomes indispensable. It has been shown to have antidepressant and anxiolytic properties in animals and humans (Zarate et al., 2004).
- Risperidone: a selective monoaminergic antagonist antipsychotic with unique properties. It has a strong affinity for serotonergic 5-HT2 and dopaminergic D2 receptors. Risperidone also binds to alpha1-adrenergic receptors and, to a lesser degree, histaminergic H1 and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, which is believed to be responsible for the beneficial effect on positive symptoms of schizophrenia, it decreases motor skills less and results in less catalepsy than conventional neuroleptics. Authorized by the FDA and the ANSM for the treatment of manic episodes in case of bipolar disorders, schizophrenia, aggressiveness in Alzheimer's disease, severe behavioral disorders of the child in case of mental retardation or autistic syndrome.
- Ropivacaine: local anesthetic of the amide type of long duration of action, with anesthetic and analgesic effects. The mechanism of action consists of a reversible decrease in the membrane permeability of nerve fibers to sodium ions. Thus, the rate of depolarization decreases, and the excitability threshold increases, inducing a local blockage of nerve impulses. Used as an anesthetic, management of severe pain and spinal anesthesia.
- Serotonin: monoamine of the indolamine family. It is found in the brain (where it acts as a neurotransmitter and neuromodulator) and in the digestive system. It is involved in the regulation of functions such as thermoregulation, eating and sexual behaviors, sleep-wake cycle, pain, anxiety or motor control. The functions of serotonin are numerous and still little described for some. It is particularly involved in the management of moods and is associated with the state of happiness when it is at a balanced rate, reducing risk-taking and thus pushing the individual to maintain a situation that is favorable to him. It is therefore essential for the survival of mammals, including humans, and has an antagonistic effect to that of dopamine which promotes, on the contrary, risk-taking and the activation of the reward system. It is, in addition, also involved in the regulation of the circadian cycle in the suprachiasmatic nucleus (seat of the circadian clock), in hemostasis, in digestive mobility and "in various psychiatric disorders such as stress, anxiety, phobias, depression". It is thus the target of certain therapeutic tools, including antidepressants, used to treat these diseases. But its activity is also modified by certain psychotropic drugs such as ecstasy.
- Sertraline: selective inhibitor of serotonin (5-HT) reuptake. It has virtually no direct effect on the reuptake of norepinephrine (NA), dopamine (DA) and gamma aminobutyric acid (GABA). Unlike most tricyclic antidepressants, Sertraline has virtually no affinity for α1-adrenergic, cholinergic (muscarinic) and histaminergic H1 receptors. In addition, it also has virtually no affinity for dopaminergic receptors D1 and D2, α2-and β-adrenergic, benzodiazepine and opioids. This selectivity of Sertraline may explain the low incidence of certain adverse reactions, including anticholinergic, sedative or orthostatic hypotension. Sold by Pfizer under

the brand name Zoloft. FDA approved in 1991 for the treatment of major depressive episodes, depressive episodes in unipolar disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder and **PTSD.**

- SNC-102: (Acamprosate) Selective NMDA glutamate receptor antagonist, and positive GABA-A receptor modulator. Medication that decreases alcohol dependence by reducing withdrawal symptoms.
- [18E] SPA-RQ: Selective antagonist of NK1 receptors related to affective and addictive disorders.
- SRX246: Vasopressin receptor antagonist (V1aR), a neuropeptide that modulates physiological and emotional responses to the threat.
- Suvorexant (Belsomra, MK-4305): authorized FDA in 2014, Merck laboratory. First representative of a new class of sleeping pills: orexin receptor antagonists. Sold under the trade name Belsomra, used in the treatment of insomnia.
- SYN117: Inhibitor of dopamine beta-hydroxylase, an enzyme that catalyzes the conversion of dopamine to norepinephrine.
- THC (tetrahydrocannabinol) or dronabinol: cannabinoid found in cannabis sativa L plants and in Indian hemp. Dsaved and isolated in 1964. Possedes psychoactive properties, acting on the psyche by modifying the cerebral rhythm. Anti-inflammatory properties. It is present in 2 drugs: Dronabinol (generic name from the International Non-proprietary name) and Sativex (used to reduce pain related to multiple sclerosis). Classified as a psychotropic substance since 1971 by the UN, banned in France since 1970 and in many countries. It is available in France through a pain center, to treat pain resistant to other drugs. In Belgium and Switzerland, the specialty Sativex is available under certain conditions. There are synthetic forms of THC such as Marinol, Syndros or analogues (related molecules) such as Nabilone. These pharmaceuticals are generally not very psychoactive. It is approved in more and more pharmacopoeias (DAB, USP ...) for various indications, such as appetite disorders certain glaucoma, sedation, treatment of chronic pain (e.g. complications related to immunity disorders). It is mainly used against vomiting and nausea in cancer patients to alleviate the side effects of chemotherapy. It is also used to increase appetite in AIDS patients .
- TNX-102 SL: developed by Tonix Pharmaceuticals currently in Phase 3 as a possible treatment for fibromyalgia and PTSD.
- Topiramate: anti-epileptic approved FDA in 1996 to treat epilepsy and migraines. Sold under the brand name Topamax by Janssen (Johnson & Johnson). Has various properties that can explain its preventive effect on epileptic seizures: decreased excitability of neurons subjected to intensive stimulation; increased activity of a substance present in the brain: gamma-aminobutyric acid (GABA); decrease in the excitatory activity of glutamate on brain receptors. In migraine sufferers, it also has the property of spacing migraine attacks, without the mechanism of action being clearly established.
- Tramadol: central analgesic whose effectiveness is due to the synergy of an opioid effect due to fixation on μ-type opioid receptors and a central monoaminergic effect due to inhibition of norepinephrine and serotonin reuptake. Used in the management of moderate to severe pain.
- Trazodone: antidepressant. Inhibitor of serotonin receptors and antagonist of 5-HT2A receptor. However, unlike selective serotonin receptor inhibitors such as fluoxetine (Prozac), trazodone's antidepressant effects may be due to its antagonistic effect at the location of the 5-HT2A receptor. It is used to treat the symptoms of depression.
- Serine: important amino acid in nervous system and immune system.
- TTI-0102: Electrochemical immunosensor of S100B associated with Trauma severity.
- Varenicline: partial agonist of the nicotinic receptors of the central nervous system. The specialty that contains this active ingredient is offered for sale worldwide under the name Champix. Its indication is the help to stop smoking smoked tobacco.
- Venlafaxine: antidepressant from the family of serotonin and norepinephrine reuptake inhibitors. Used in the treatment of depressive states and to prevent depressive recurrence in people who have already had several

episodes of depression and in certain manifestations of anxiety (generalized anxiety, social phobia, panic attacks).

- Vilazodone: antidepressant marketed as ViiBryd.
- Vortioxetine: antidepressant. Mechanism of action of Vortioxetine is thought to be related to the direct modulation of serotonergic receptor activity and inhibition of the serotonin transporter (5-HT). Non-clinical data indicate a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, a partial 5-HT1B receptor agonist, a 5-HT1A receptor agonist and a 5-HT transporter inhibitor, leading to neurotransmission modulation in multiple systems. These are mainly serotonin, but probably also norepinephrine, dopamine, histamine, acetylcholine, GABA and glutamate. This multimodal activity is believed to be responsible for the antidepressant and anxiolytic effects as well as the improvement of cognitive function, learning and memory observed with Vortioxetine in animals. Indicated in major depression.
- Xenon: inhalation of xenon for the treatment of PTSD and panic disorders in a phase II clinical trial. Is being tested in phase I on Parkinson's disease. Developed by Nobilis Therapeutics, acts as NMDA receptor antagonist. Therapeutic class: anti-dementia, antiparkinsonian, anxiolytic, behavioral disorder therapy, therapy against irritable bowel syndromes.
- Xyrem: anesthetic that acts on the central nervous system. Its mechanism of action is poorly understood. Taken before falling asleep, it increases deep sleep and the duration of night sleep. It thus reduces excessive drowsiness during the day. Indicated for narcolepsy and hypersomnia.
- Yohimbine: selective inhibitor of presynaptic, sympatholytic, vasodilator and hypotensive alpha2-adrener receptors. Orthostatic hypotension treatment, erectile insufficiency.
- Ziprasidone: antidepressant developed by Clinical Data for the treatment of major depression, marketed as ViiBryd. In 2009, the product performed well in two Phase III clinical trials. The product obtained its MA from the FDA in January 2011. Antagonist of serotonin receptors type 2A (5HT2A) and dopamine receptors type 2 (D2). Exact mechanism of action is unknown; however, antipsychotic activity would be average, partly due to this combination of antagonistic effects. It is also a potent antagonist of the 5HT2C and 5HT1D receptors and inhibits the neuronal reuptake of norepinephrine and serotonin. Management of acute agitations in case of psychosis.
- Zonisamide: sulfonamide, sold under the brand name Zonegran, used to treat the symptoms of epilepsy and Parkinson disease.

Appendix 3: Clinical trial base by molecule, phase and period

Highlighted in green -> considered abandoned.
Highlighted in yellow -> biomarker.
Highlighted in blue -> allowed in PTSD support.

Caution: the classification of phase (1 2 3 4) has not been established by ReST but is the one which is registered by the sponsor itself on ClinicalTrial.gov.
Strictly speaking, except for Sertraline and Paroxetine, there should not be any registered phase 4 trials. All the other "phase 4 trials" with drugs already marketed, but already marketed for other clinical indications, should rather have been recorded as phase 3, possibly phase 3b (or even phase 2 for some of them, depending on the exact study design and protocol).

Period 2015-2022

	Drug 1	Drug 2	Nb studies
Phase 4	Suvorexant		2
	Venlafaxine		2
	Pimavanserin		2
	Prazosin		2
	Oxytocin		1
	Vortioxetine		1
	L-DOPA		1
	Mianserin		1
	Minocycline		1
	Ketamine	Fentanyl	1
	THC		1
	Ramelteon		1
	Propranolol		1
	Sertraline		1
	Escitalopram	Duloxetine	1
	Eszopiclone		1
Phase 3	TNX - 102 SL		4
	Ketamine		2
	Propranolol		2
	Brexpiprazole		2
	Pregabalin		1
	Prazosin		1
	Estradiol		1
	MDMA		1
	Trazodone		1
	Dexmedetomidine		1
	Clonidine		1
Phase 2	MDMA		8
	Oxytocin		7

	Ketamine	7
	Propranolol	5
	Prazosin	4
	THC	3
	THC et CBD	3
	Oxytocin	3
	CBD	2
	N-Acetylcysteine	2
	Doxazosin	2
	Brexpiprazole	3
	Topiramate	2
	NYX-783	2
	Nitrous Oxide	2
	BNC210	2
	Methylphenidate	2
	Buprenorphine	2
	Hydrocortisone	2
	TNX - 102 SL	1
	SRX246	1
	Progesterone	1
	SNC-102	1
	DHEA	1
	Pregnenolone	1
	Zonisamide	1
	L-DOPA	1
	Lofexidine	1
	BI 1358894	1
	JZP150	1
	ALTO-100	1
	NBTX-001 Xenon	1
	CORT108297	1
	Insulin	1
	Losartan	1
	Paroxetine	1
Phase 1	Ketamine	6
	CBD	2
	Psilocybin	2
	Dexmedetomidine	2
	THC	2
	MDMA	2
	Ropivacaine	2
	Fluorodeoxyglucose	1
	Lipopolysaccharide	1
	Riluzole	1
	Dexamethasone	1

Lanicemine		1
Aleozen		1
Estradiol		1
Quetiapine		1
Neuropeptide Y		1
Lu AG06466		1
[11C] MK-3168		1
Pregnenolone		1
Trazodone		1
TTI-0102		1
PT150		1
Brexanolone		1
Propranolol	Prazosin	1
Fluoxetine		1
Hydrocortisone		1

Table 11: List of molecules tested in clinical trials in the "drug" category from 2015 to 2022 on PTSD classification by phase of the clinical trial

Period before 2015

	Drug 1	Drug 2	Nb of studies
Phase 4	Paroxetine		11
	Sertraline		10
	Propranolol		8
	Prazosin		8
	Topiramate		6
	Hydrocortisone		6
	Ziprasidone		2
	Quetiapine		2
	THC		2
	Mirtazapine	Sertraline	2
	Eszopiclone		2
	Risperidone		1
	Divalproex		1
	Prednisone		1
	Memantine		1
	Escitalopram		1
	Paliperidone		1
	Mifepristone		1
	Fluoxetine		1
	Syntocinon		1
	Tramadol		1
	Vilazodone		1
	Asenapine		1
	Venlafaxine		1
	Diazepam		1
	Doxazosin		1
	Haloperidol		1
	Atomoxetine		1
	Pramipexole		1
	Phenytoin		1
Phase 3	Paroxetine		3
	Quetiapine		3
	Escitalopram		3
	Sertraline		2
	Prazosin		2
	Topiramate		1
	Fluoxetine		1
	Divalproex		1
	Aripiprazole		1
	Duloxetine		1
	D-Cycloserine		1
	Propranolol		1

	Brexpiprazole		1
Phase 2	Propranolol		7
	MDMA		10
	D-cycloserine		6
	Oxytocin		3
	Hydrocortisone		3
	Paroxetine		2
	Sertraline		2
	Ketamine	Midazolam	2
	Prazosin		2
	Pregnenolone		2
	N-Acetylcysteine		2
	Mifepristone		2
	GSK561679		2
	SYN117 (Nepicastat)		2
	Sertraline		1
	Enbrel		1
	Topiramate		1
	D-Serine		1
	Levetiracetam		1
	Xyrem		1
	Risperidone		1
	Aripiprazole		1
	Escitalopram		1
	Methylene Blue		1
	Orvepitant		1
	Aprepitant		1
	Varenicline		1
	Yohimbine		1
	Carvedilol		1
	Methylphenidate		1
	Ganaxolone		1
	Atorvastatin		1
	Modafinil		1
	Oxygen		1
	Keto Dehydroepiandrosterone		1
	Iloperidone		1
	PF-04457845		1
	TNX - 102 SL		1
	Dobutamine		1
	Desvenlafaxine		1
	Omega-3		1
	Bupropion		1
	Fluticasone propionate 2		1
	Buprenorphine		1

	Rapamycin		1
Phase 1	Ketamine		3
	Riluzole		2
	Mifepristone		2
	Nicotine patch		2
	Dexamethasone		2
	Pomaglumetad Methionil		1
	Duloxetine		1
	[18F] SPA-RQ		1
	Oxygen		1
	Dexmedetomidine	Propofol	1
	Lithium Carbonate		1
	[C-11] MENET		1
	Neuropeptide Y		1
	Doxazosin	Perindopril	1
	Ifenprodil		1
	Methylphenidate		1
	Hydrocortisone		1
	PRX-03140		1
	Seromycin		1
	Cortisol		1
	Guanfacine		1

Table 12: List of molecules tested in clinical trials in the "Drug" category before 2015 on PTSD classification by phase of the clinical trial

Appendix 4: Fact sheet on start-ups and biotechs

ALTO NEUROSCIENCES, Los Altos, California, USA

SHAREHOLDERS-INVESTORS	**Institutions** : Stanford University **VC/Investment Funds** : Apeiron Investment Group (Lead), Able Partners, Presight Capital, Windham Venture Partners, What if Ventures, Korify Capital, Risk and Return **Private Investors** : Tim Kendall (Seed Round)
TEAM	**Amit Enabled** (M.D, Ph.D Stanford Univ.): Founder and CEO; Prof. at Stanford Univ. **Dan Segal** (BSc, MSc): Founder and COO; Ex-Deutsche Bank, ex- Citigroup **Wei Wu** (Ph.D) ; Founder and CDO; Ex Prof. at Stanford Univ. **Adam Avitz** (M.D/Ph.D UCLA) : CMO, ex-Janssen (psychiatry consortia: IMI's EU-PEARL and fNIH's AMP-Sz)
FINANCE OVERVIEW	Market Capitalization: - Share Price: -
CAPITAL RAISED	Seed Round: $8M (2019) Series A: $32M (2021)
PRODUCT OVERVIEW	**Central Nervous System**: An Open-label Study of **ALTO-100** in Adults with Major Depressive Disorder and/or Post-traumatic stress disorder (MDD and/or PTSD): Phase II **Central Nervous System**: An Open-label Study of **ALTO-300** in Adults with Major Depressive Disorder (Depression): Phase II **Biomarkers Platform - AI**: Biomarkers platform with a tight focus on core domains of mental functioning (cognition, emotion, and sleep) and their underlying brain circuits + Genomics
News - Publications	-Cerebral and Alto Neuroscience enter into Strategic collaboration to Launch First-Ever Decentralized Study in Precision Psychiatry. -Alto Neuroscience Announces Publication in Nature Neuroscience Highlighting Superiority of Data-Driven Framework for Mapping Human Neurobiology Domains. -Alto Neuroscience Emerges with Largest Clinical-Stage Precision Psychiatry Pipeline and $40 Million in Financing.

Hydra Biosciences, Cambridge, Massachusetts, USA

SHAREHOLDERS-INVESTORS	**Institutions**: - **VC/Investment Funds**: Polaris Partners, Advanced Technology Ventures, Lilly Ventures, MedImmune Ventures, Abingworth, Biogen Idec **Private Investors**: -
TEAM	**Russell Herndon** (BS): CEO, ex-Sanofi (Genzyme) **Russell Smith** (Ph.D, Columbia) **:** CTO
FINANCE OVERVIEW	Market Capitalization: - Share Price: -
CAPITAL RAISED	Seed Round: $200K (2001) Series C: $34M (2008) Series A: $9.3M (2002) Series D: $22M (2009) Series B: $18.9M (2004) Series E: $10.5M (2015)
PRODUCT OVERVIEW	**Central Nervous System**: A Study to Test Whether Taking **BI 1358894** for 8 Weeks Helps Adults with Post-traumatic stress disorder: Phase II (**Hydra Biosciences/Boehringer Ingelheim**) **TRP (Transient Receptor Potential) family of ion channels Platform**: **Eli Lilly and Company** (NYSE: LLY) today announced an agreement with Hydra Biosciences to acquire all assets related to Hydra's pre-clinical program of TRPA1 antagonists, part of the Transient Receptor Potential (TRP) family of ion channels
News - Publications	-A Study to Test Whether Taking BI 1358894 for 8 Weeks Helps Adults With Post-traumatic Stress Disorder - Full Text View - ClinicalTrials.gov -TRPC4/5 Inhibitor Now Investigated in Clinic for Central Nervous System Disorders -Lilly to Acquire Pre-Clinical Pain Program from Hydra Biosciences of Data-Driven Framework for Mapping Human Neurobiology Domains.
Investors	This prominent group of investors includes Abingworth Ventures, Advanced Technology Ventures, Polaris Ventures, Lilly Bio Ventures, New Enterprise Associates, BioVentures Investors, Biogen Idec, Boston Medical Investors, and MedImmune Ventures

Bionomics, Thebarton, South Australia, Australia

SHAREHOLDERS-INVESTORS	**Institutions**: - **VC/Investment Funds**: Novamind, Start-up Australia Ventures **Private Investors**: -
TEAM	**Dr.Errol De Souza** (Ph.D): Executive Chairman; ex-CEO (Biodel, Synaptic Pharmaceutical, Archemix Corp, Neuropore Therapies), ex-founder Neurocrine Biosciences, ex-SVP Aventis, ex-SVP R&D at DuPont Merck **Adrian Hiton** (BEc, FCA): CFO; Ex-Deloitte **Connor Bernstein** (MSc: VP Strategy & Corporate Development, ex-RBC Capital, ex-Perella Weinberg Partners, ex-Guggenheim, ex- Piper Jaffray
FINANCE OVERVIEW	Market Capitalization: $68M Share Price: $0.05
CAPITAL RAISED	Post IPO Equity: $10.1M (2009), $10.4M (2012), $22.9M (2021)
PRODUCT OVERVIEW	**Central Nervous System** BNC210 for PTSD and SAD (Social Anxiety Disorder): Phase II BNC210 + EMP-01 (EmpathBio – Atai Life Sciences) for PTSD: PreClinical α7 Receptor PAM + MERCK, 2 candidates for cognitive deficits in AD: Preclinical & Phase 1
News - Publications	-Joint feasibility assessment of Bionomics' BNC210 and EmpathBio's MDMA derivative EMP-01 treatment regimen for PTSD (atai.life) -Bionomics Signs Option and License Agreement with Merck

Corcept Therapeutics, Menlo Park, California, USA

SHAREHOLDERS-INVESTORS	**Institutions**: **VC/Investment Funds**: Sutter Hill Ventures, Alta Partners, Longitude Capital, Paperboy Ventures **Private Investors**:
TEAM	**Joseph Belanoff** (M.D, Columbia): CEO; ex-Stanford University - Psychiatry **Hazel Hunt** (BSc, Ph.D): CSO; Ex-Celltech, ex- GSK, ex-Argenta **Charlie Robb** (BA, JD Harvard); Chief Business Officer **William Guyer** (PharmD): Chief Development Officer, ex-SVP Gilead **Sean Maduck** (BE, MSM Stanford): Chief Commercial Officer, ex-Genentech
FINANCE OVERVIEW	Market Capitalization: $2.55B Share Price: $24.12
CAPITAL RAISED	Venture Rounds: $28M (2001), $12.8M (2002) Post-IPO Equity: $3M (2006), $10.1M (2007), $18M (2009), $7.7M (2010)

PRODUCT OVERVIEW

Endocrine & Metabolic	**Relacorilant:** Phase II (1), Phase III (2) **Miricorilant**: Phase II (2), Phase I (1)
Oncology	**Mifepristone**: Phase II (3) **Relacorilant**: Phase I (1), Phase II (2)
Neurology	**CORT113176**: Phase 1
Addiction	**Mifepristone**: Phase II
Psychiatry	**CORT108297**: Phase II

News - Publications	

Nobilis Therapeutics, Portland, Oregon, USA

SHAREHOLDERS-INVESTORS	**Institutions**: Stanford University **VC/Investment Funds**: Apeiron Investment Group (Lead), Able Partners, Presight Capital, Windham Venture Partners, What if Ventures, Korify Capital, Risk and Return **Private Investors**: Tim Kendall (Seed Round)
TEAM	**Dr. Vlad Bogin** (M.D: CEO; ex-Boehringer Ingelheim, ex-Chairman Medistem **Alexander Dobrovolsky** (MD, Ph.D): Core Expert **Dr. Yan Stillman**; Chief Business Officer; Ex-CEO of the California Chapter of the Russian American Dental Association
FINANCE OVERVIEW	Market Capitalization: - Share Price: -
CAPITAL RAISED	Seed Round: - Series A: -
PRODUCT OVERVIEW	**Psychiatry**: NBTX-001 for PTSD (Phase 2b) NBTX-001 for panic disorder (PD): Phase IIb **Neurodegenerative**: Parkinson's disease: Phase I
News - Publications	

Aptinyx, Evanston, Illinois, USA

SHAREHOLDERS-INVESTORS	**Institutions**: **VC/Investment Funds**: Longitude Capital, K2 HealthVentures, LVP Life Science Ventures, New Leaf Venture Partners, Bain Capital Life Sciences **Private Investors**:
TEAM	**Norbert G.Riedel** (Ph.D): Executive Chairman; ex CEO Naurex, ex Baxter, ex Sanofi. board member Jazz Pharma and Cerevel Therapeutics. **Andy Kidd** (MD): CEO; Ex-BCG, ex- Baxter (GM Canada) **Ashish Khanna** (MBA) ; CFO, ex-EY, ex Naurex, ex J&J
FINANCE OVERVIEW	Market Capitalization: $186M Share Price: $2.75
CAPITAL RAISED	Seed A: $65M (2016) Series B: $70M (2017) Post-IPO Equity/Secondary: $35M (2020), $48.3M (2020), $50M (2021)
PRODUCT OVERVIEW	**Central Nervous System**: NYX-2925: Painful Diabetic, Peripheral Neuropathy (Phase II) NYX-2925: Fibromyalgia (Phase II) NYX-783 for PTSD (Phase II) NYX-458 for Cognitive Impairment in Parkinson's Disease & Dementia with Lewy Bodies (Phase II)
News - Publications	-Aptinyx-Highlights-Key-Goals-and-Anticipated-Development-Milestones-for-2022-2022.pdf (q4cdn.com) -Aptinyx-Initiates-Phase-2b-Study-of-NYX-783-in-Patients-with-Post-Traumatic-Stress-Disorder-2021.pdf (q4cdn.com)

Predix Pharmaceuticals (acquired by Epix Pharmaceutical),

Boston Massachusetts, USA

SHAREHOLDERS-INVESTORS	**Institutions**: **VC/Investment Funds**: OrbiMed, Yozma Group, Boston Millennial Partners, CMEA Ventures, Forward ventures, JAFCO Asia **Private Investors**:
TEAM	**Chen Schor:** Chief Business Officer
FINANCE OVERVIEW	Market Capitalization: - Share Price: -
CAPITAL RAISED	Series B: $820K (2003) Series A: $10.8 : $3M + $7M (2000,2001) Series C: $43M (2005)
PRODUCT OVERVIEW	**Central Nervous System**
	PRX-00023: receptor full agonist (later discovered to be an antagonist) for major depression and generalized anxiety disorder **PRX-03140**: receptor partial agonist: for Alzheimer's disease PRX-07034: receptor antagonist: for obesity and cognitive impairment associated with Alzheimer's disease and schizophrenia PRX-08066: receptor antagonist: for pulmonary hypertension associated with chronic obstructive pulmonary disease
News - Publications	-EPIX Pharmaceuticals And Predix Pharmaceuticals Announce Merger Agreement In $90 Million Stock Deal | BioSpace
Investors	Boston Millenia Partners, CMEA Ventures, forward ventures, yozma group

Pop Test & Palisades Therapeutics Companies, Cliffside Park, NJ, USA

SHAREHOLDERS-INVESTORS	**Institutions**: **VC/Investment Funds**: **Private Investors**:
TEAM	**Randi Altschul:** CEO **Neil Theise** (MD): Lead Scientist **Robert Foerster**: CFO, ex-Pfizer **John M.H. Gregg** (MBA): COO, ex Pfizer, ex-Novartis, ex-J&J
FINANCE OVERVIEW	Market Capitalization: - Share Price: -
CAPITAL RAISED	Seed Round: Series A:
PRODUCT OVERVIEW	**Central Nervous System**
News - Publications	-ttps://www.einpresswire.com/article/560820192/palisades-therapeutics-drug-platform-demonstrates-reduction-in-neuroinflammation-across-three-species

Synchroneuron, Newton, Massachusetts, USA

SHAREHOLDERS-INVESTORS	**Institutions**: **VC/Investment Funds**: Morningside Group **Private Investors**:
TEAM	**William D Kerns** (): Founder and CEO. **Barry S. Fogel** (MD): Founder and CSO; Clinical Professor of Psychiatry at Harvard Medical School **Kei-Lai L. Fong** (); Founder and SVP, Development.
FINANCE OVERVIEW	Market Capitalization: - Share Price: -
CAPITAL RAISED	Series A: $20M (2014) Series B: $6M (20212
PRODUCT OVERVIEW	**Central Nervous System**
	SNC-102: for moderate to severe tardive dyskinesia (TD): Phase II SNC-102 for PTSD and Tourette syndrome: Phase II
News - Publications	-Synchroneuron Raises $20 Million in Series B to Fund Continued Development of SNC-102 for Neuropsychiatric Disorders | Business Wire
Investors	Morningside ventures, Morningside venture capital

Biotie Therapies, Turku, Finland

SHAREHOLDERS-INVESTORS	**Institutions**: **VC/Investment Funds**: OrbiMed Advisors, Versant Ventures, Vivo Capital **Private Investors**: Michael J.Fox Foundation
TEAM	**William Burns** (B.A): Director. Ex CEO of Pharmaceutical Division of Hoffman-La Roche **Kai Lahdesmaki** (): CBO **Steve Bandak** (): CMO
FINANCE OVERVIEW	Market Capitalization: - Share Price: -
CAPITAL RAISED	Post IPO Equity: €18.8M (2006), €27M (2011), €30M (2012), $143.8M (2013), $6.1M (2015)
PRODUCT OVERVIEW	**Central Nervous System**: SYN120: Parkinson SYN120: PTSD Tozadenant: Parkinson (Phase 3)
News - Publications	-Acorda Therapeutics Inc - Acorda to Acquire Biotie Therapies

Azevan Pharmaceuticals, Bethlehem, Pennsylvania, USA

SHAREHOLDERS-INVESTORS	**Institutions**: - **VC/Investment Funds**: - **Private Investors**: -
TEAM	**Dr. Neal G Simon** (MS, Ph.D):CEO; **Dr. Michael Brownstein** (): SVP, Drug Development, worked with Julius Axelrod (Nobel Prize 1970), NIH, ex Chief of the Laboratory of Genetics of the National Institute of Mental Health. **Eve M.Damiano** (MS): VP Operations, ex-MedImmune, ex-OraSure Technologies, ex-Vicuron Pharmacueticals
FINANCE OVERVIEW	Market Capitalization: - Share Price: -
CAPITAL RAISED	Venture Round: $2.2M (2013)
PRODUCT OVERVIEW	**Central Nervous System**: SRX246: Huntington's Disease patients with irritability and for the treatment of Intermittent Explosive Disorder (Phase II) SRX246: Phase II clinical trial for the treatment of PTSD is in progress SRX251: reduce measures of stress, fear, aggression, depression, and anxiety in preclinical models
News - Publications	-JCM | Free Full-Text | Safety and Tolerability of SRX246, a Vasopressin 1a Antagonist, in Irritable Huntington's Disease Patients—A Randomized Phase 2 Clinical Trial (mdpi.com) -The National Institute of Neurological Diseases and Stroke awarded a Commercialization Readiness Pilot Program grant to Azevan in September 2020. The award, which builds on a previous SBIR Phase 2 project that supported the recently completed Phase 2 trial, "Safety, Tolerability, and Activity of SRX246 in Irritable Subjects with Huntington's Disease" - Phase 2 trial results were recently published in Journal of Clinical Medicine. The paper presents the data for the primary endpoint, tolerability, and the key secondary

Thiogenesis Therapeutics, Belmont, Massachusetts, USA

SHAREHOLDERS-INVESTORS	**Institutions**: **VC/Investment Funds**: **Private Investors**:
TEAM	**Patrice P. Rioux** (MD): Vice President-Medical Research at Repligen Corp., Chief Medical Officer for Edison Pharmaceuticals, Inc., Chief Medical Officer of Raptor Pharmaceuticals Corp., Chief Medical Officer of FerroKin BioSciences, Inc., Chief Medical Officer for Horizon Pharmaceutical LLC, Chief Medical Officer for Raptor Pharmaceuticals, Inc., Chief Medical Officer at Monopar Therapeutics, Inc. and Senior Vice President-Global Clinical Development at ArmaGen, Inc.
FINANCE OVERVIEW	Market Capitalization: - Share Price: -
CAPITAL RAISED	Seed Round: Series A:
PRODUCT OVERVIEW	**Central Nervous System**

News - Publications

-TTI-0102 for Veterans With TBI - Full Text View - ClinicalTrials.gov

Appendix 5: Method of search

Intellectual properties searches

The search was conducted on patent documents exclusively interested on PTSD (its prevention and its treatment) or directly related symptoms. To do this, the keywords were defined as follows in the title and abstract of documents:

((post_trauma*) W2 STRESS) OR PTSD AND ALIVE=(YES)→ *corresponds to the search for post-traumatic stress [disease/condition/disorder/syndrome etc...] according to different spellings (dash/space or not etc. ...)*

"Wx" words separated from at most W words, regardless of order
"": 0 or infinite string of characters*
"_": optional separation (space, dash, or no space)

Results of the search was presented in an excel table and analyzed to be classified per:

- Assignee
    - Academic: university, foundation, or any other non-profit structure
    - Industrial: industry name clearly mentioned
    - Individual: only the name of a person mentioned
    - patent layer: only the name of a patent layer mentioned
- and category of patent
    - API: patent with a pharmaceutical compound which clearly mentioned PTSD or suggest that PTSD is applicable (narcotics excluded)
    - Narcotics: patent on narcotics which clearly mentioned PTSD or suggest that PTSD is applicable
    - Other: patent on all intervention which is not an API (and narcotics) which clearly mentioned PTSD or suggest that PTSD is applicable (device, behavioral, …)
    - Non relevant: clearly not related to PTSD