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PULLAN'S PIECES, PART II

A BUSINESS DEVELOPMENT LOOK AT THE CNS LANDSCAPE

By Linda M. Pullan, PhD, Pullan Consulting

The unmet needs in CNS are huge. With one hundred million Americans affected by neurological disorders and 43 million Americans suffering from some type of mental illness, the societal impact of CNS afflictions is astronomical. There may be no other therapeutic area where the unmet needs are bigger. What's more, these diseases are often accompanied by a "loss of self," which in itself is devastating.

100M & **43.4M**
Americans affected by neurological disorders (MID Report 2018) & American adults have a mental illness (MID Report 2017)

The numbers of indications with drugs in development are also impressive, both in the categories of neurology and psychiatry.

Indications shown in orange have over 7 million patients.

Neurology

Chronic Neurological

- Alzheimer's
- Chronic Inflammatory Demyelinating Polyneuropathy
- Complex Regional Pain Syndrome
- Dyskinesia
- Epilepsy
- Fibromyalgia
- HD
- MCI
- Migraine
- MS
- Multi-focal Motor Neuropathy
- Neuropathic Pain
- NMO
- PD
- Trigeminal Neuralgia

Acute and Semi-Acute

- Cancer pain
- Cataplexy
- Guillain-Barré
- Headaches
- Pain
- Stroke
- TBI

Orphan Neurology

- ALS
- Ataxias
- Batten Disease
- Broca Aphasia
- Canavan Disease
- Carnosinemia
- Cerebral Palsy
- Dravet Syndrome
- Friedreich Ataxia
- Globoid Cell Leukodystrophy
- Syringomyelia
- Tardive Dyskinesia
- Hyperkalemic Periodic Paralysis
- Kluver-Bucy Syndrome
- Lennox Gastaut
- Meige's Syndrome
- Metachromatic Leukodystrophy
- Pick Disease
- Rett Syndrome
- Schindler Disease
- Simian B Virus Infection
- SMA

Psychiatry

- ADHD
- Alcohol addiction
- Anorexia Nervosa
- Autism
- Binge eating
- Bipolar Disorder
- Dementia
- Depression
- Insomnia
- Narcolepsy
- Panic Disorder
- PTSD
- Schizophrenia
- Tourette Syndrome

HOW DOES THE CNS LANDSCAPE COMPARE TO THAT OF CANCER?

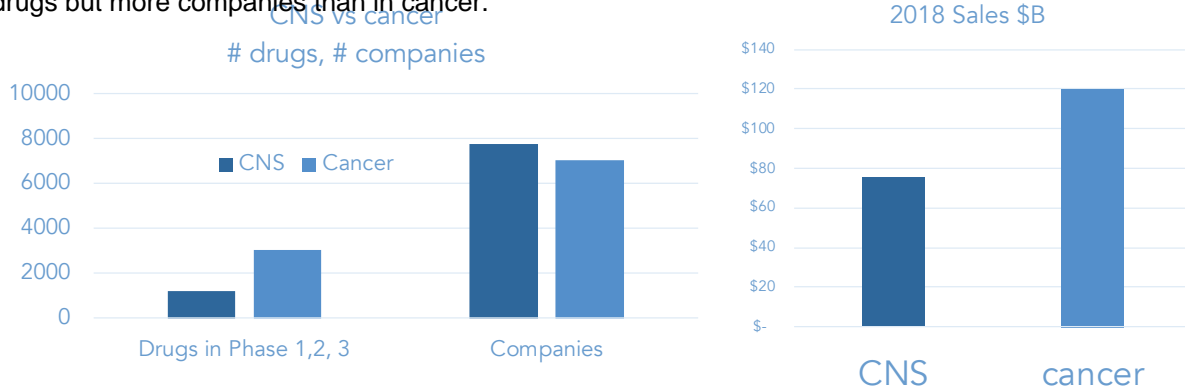
Compared to cancer, there are more companies focused on CNS, but there are fewer drugs in Phase I, II, and III. Presumably, this means that many of the CNS companies are young and work in the preclinical and discovery phases.

this headline only applies to the right graph.

The left graph **Sales in CNS Are Big, But Smaller Than Cancer**

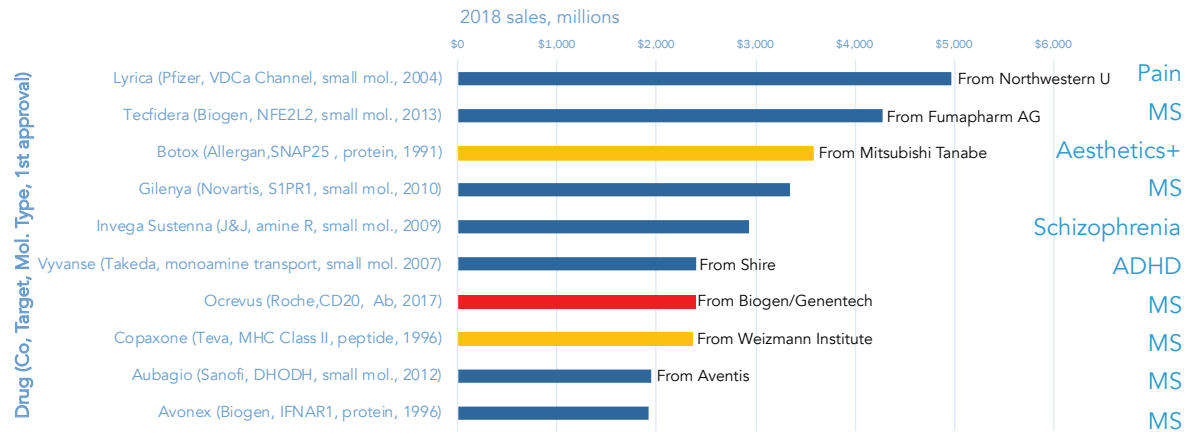
could have a caption of

Fewer CNS drugs but more companies than in cancer.



Sales in CNS represent about 7.5% of all pharmaceutical sales. A majority of the sales (55%) are in the US, which is a larger percentage compared to the percentage of sales in the US for the pharmaceutical industry as a whole, which is about 40%.

2018: Top 10 Drug Sales



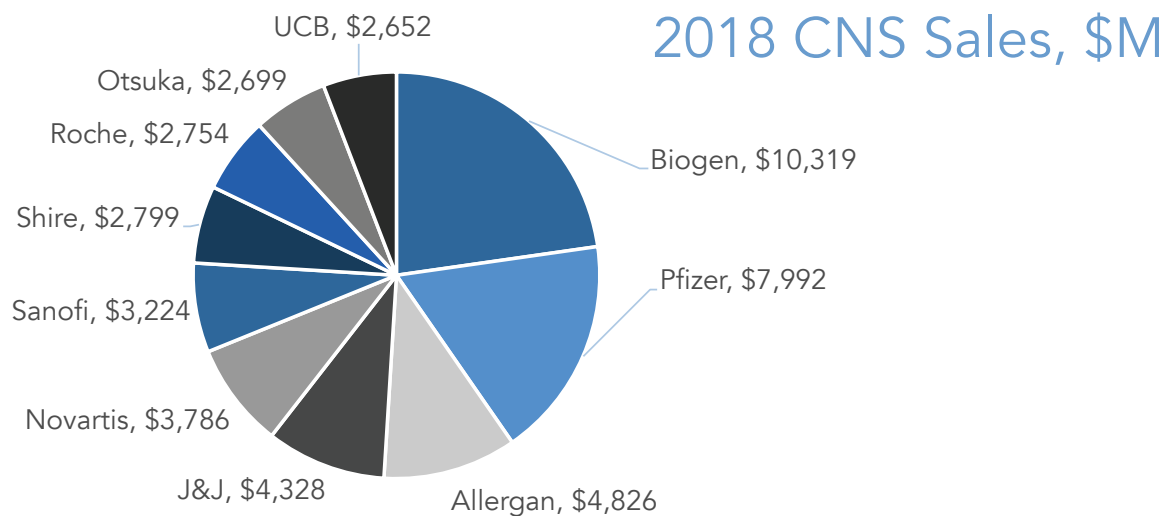
The magnitude of sales in CNS is significant. To make the top ten list, sales must be over \$1.7 billion. From this chart, we can see that there is a heavy emphasis on multiple sclerosis. Also, there are a few peptides and proteins (yellow bars) and an antibody (red bar), but most drugs being marketed for CNS are small molecules. Interestingly, most of the molecules are the result of a licensing deal, partnership, or

missing space after (yellow bars)

M&A deal. This highlights the tremendous reliance of the pharmaceutical industry on dealmaking and alliances.

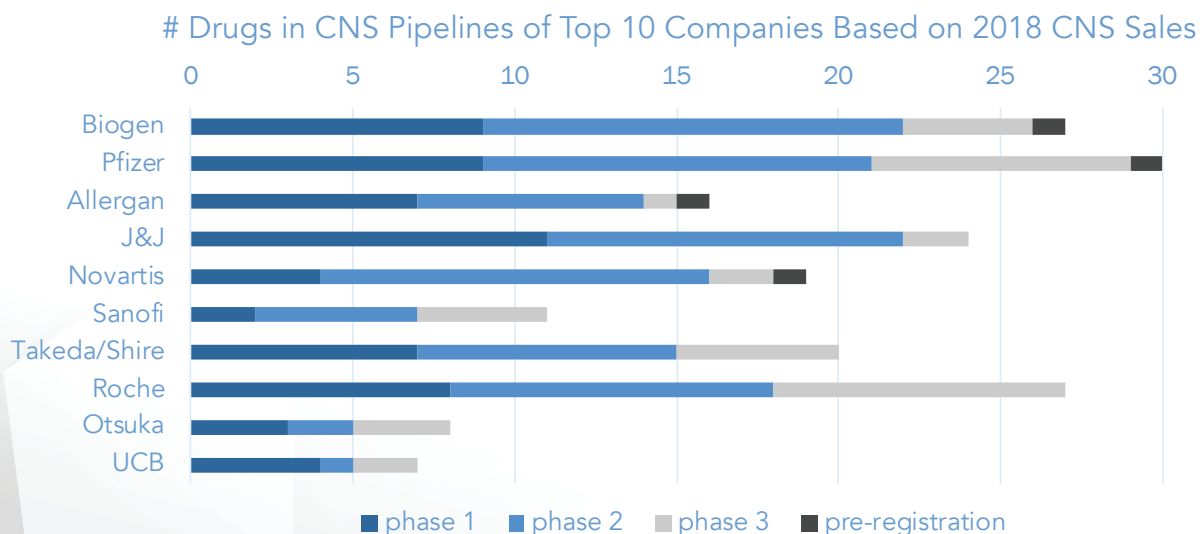
Also of note are the first approval dates, some of which are quite old, with first approvals in 1991 and 1996. Yet these early approved drugs are still leading in sales, indicating that it's possible to build very large sales in CNS and hold on to them for many years.

2018: Top 10 Companies

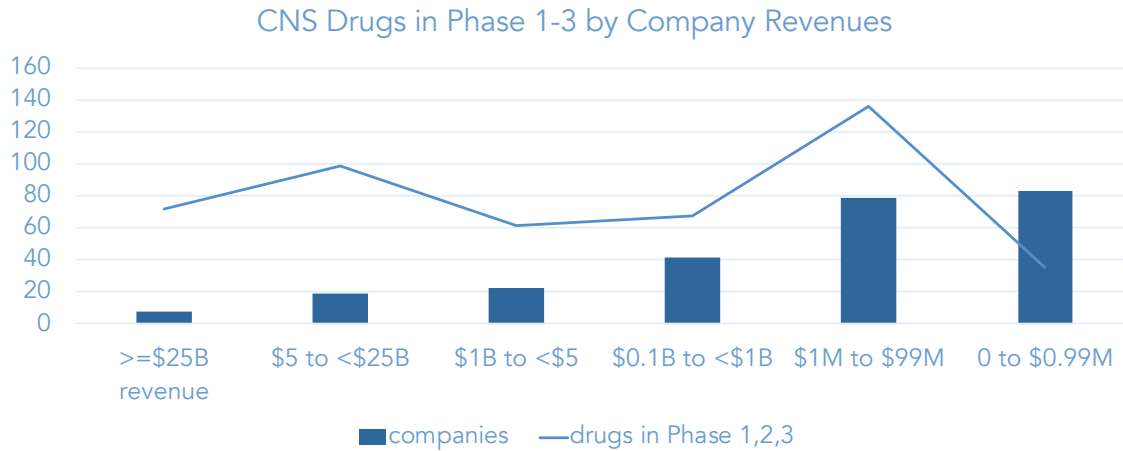


Again, we see from this chart that sales in CNS are significant. To make the top 10 list of companies, sales must be at least \$2.6 billion. Biogen leads the industry with over \$10 billion in sales.

WHAT'S IN THE PIPELINE?



When looking at clinical development pipelines, we see that Biogen, Pfizer and Roche have pretty healthy pipelines. UCB, Otsuka and Sanofi, have leaner pipelines. With attrition rates what they are, it takes a lot of molecules to maintain healthy sales. Based on this data, it may be challenging for most of these companies to keep their top-10 slot.



Interestingly, most pipeline drugs are not being developed by the top 10 companies. This chart shows that there are a great deal of drugs in small companies and those with no revenue. This situation presents many potential opportunities for partnering.

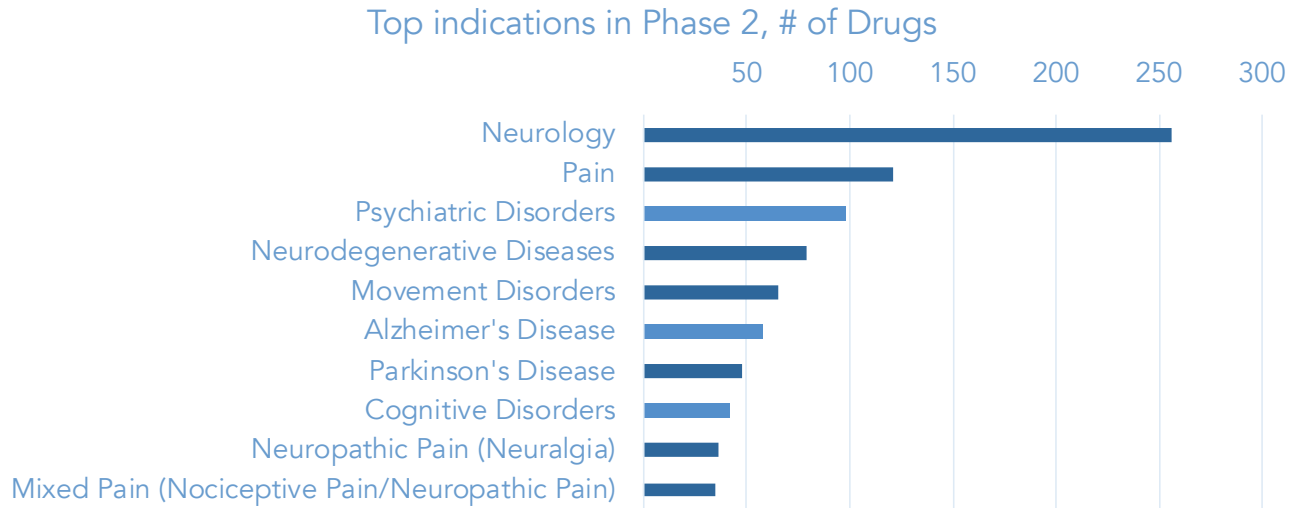
PROBABILITY OF SUCCESS BY STAGE

When looking at success rates by stage, it’s apparent that CNS is a tough segment of drug development. The likelihood of approval of all therapeutic areas combined is above 17%, but all CNS categories are much lower.

	Phase 1	Phase 2	Phase 3	Registration to Approval	Overall LOA
Neurology/CNS	63.6%	36.2%	54.8%	85.1%	10.7%
Psychiatry	57.0%	23.5%	59.5%	84.8%	6.7%
CNS Orphan	85.0%	56.3%		32.0%	5.0%
All Therapeutic Areas	70.6%	47%	61.8%	84.6%	17.3%

<https://www.alacrita.com/whitepapers/pharmaceutical-probability-of-success>

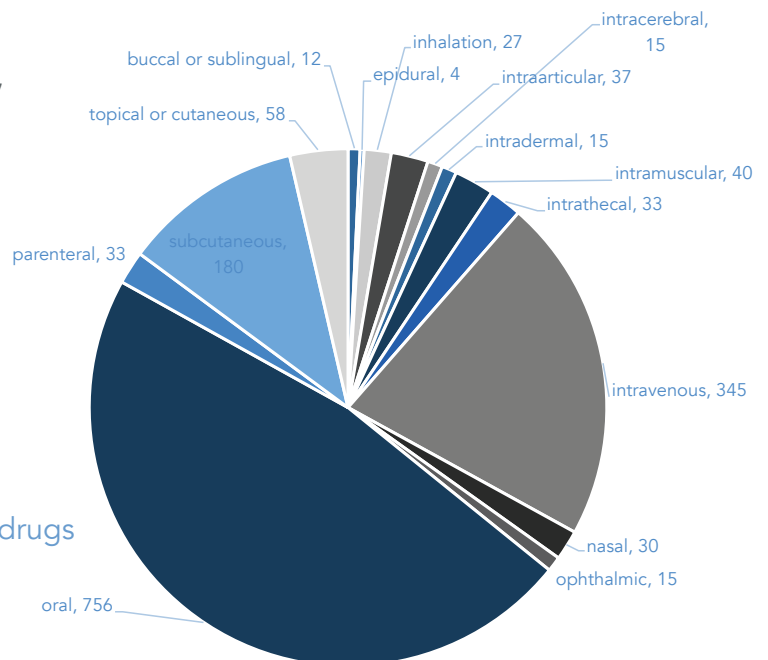
TOP CNS INDICATIONS IN PHASE II



If indications in Phase II are indicative of what's to come, we see that most of the solutions are focused on neurology, not psychiatric disorders. Despite the unmet need, not a lot of psychiatric drugs are being developed. Pain is a significant focus, as are neurodegenerative diseases, Parkinson's, Alzheimer's and cognitive disorders.

ROUTES OF ADMINISTRATION

The routes of administration of Phase II CNS drugs are impressively varied. Oral is the dominant category, with intravenous and subcutaneous second and third. But observe the numerous specialized routes, such as intrathecal, intracerebral, as well as intramuscular, inhalation, and ophthalmic. There are remarkable diverse routes of administration being employed.



should be remarkably not remarkable

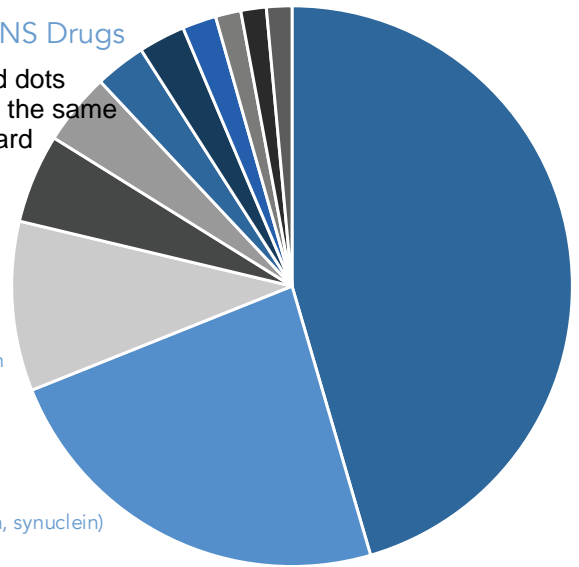
TARGET CLASSES

The target classes are perhaps less varied than one would expect. Receptors, enzymes, and ion channels dominate. Transporters have historically been a big category, but it's a relatively small chunk in Phase II. Amyloid and tau are still a significant chunk. Cytokines, membrane proteins, and nerve proteins make up the rest.

Target Classes in Phase 2 CNS Drugs

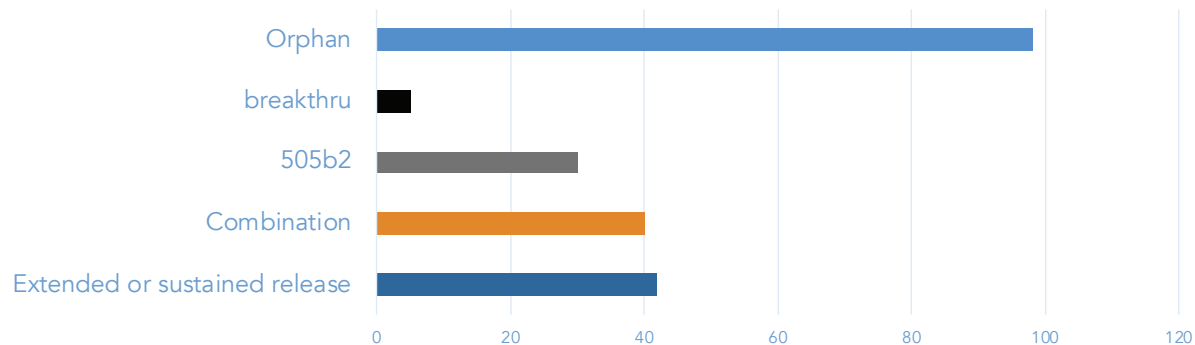
Can you make the legend dots larger? with these almost the same color dots, they can be hard to trace to the pie

- receptor
- enzyme
- ion channels
- transporter
- other
- amyloid
- tau and cytoskeleton
- growth factor
- cytokines
- membrane protein
- nerve protein (ataxin, synuclein)



DESIGNATIONS FOR CNS PHASE II DRUGS

Designations for CNS Phase 2 drugs (474 total)



Orphan drugs comprise about 20% of Phase II CNS drugs (100 out of 474). Breakthrough designations are fairly rare, and 505b2, where the data from an existing drug is used to substantiate a new formulation of that drug, makes up a significant portion. Combinations are also a significant portion, but much less so than in oncology. Finally, extended or sustained release drugs comprise a surprisingly small piece of CNS designations.

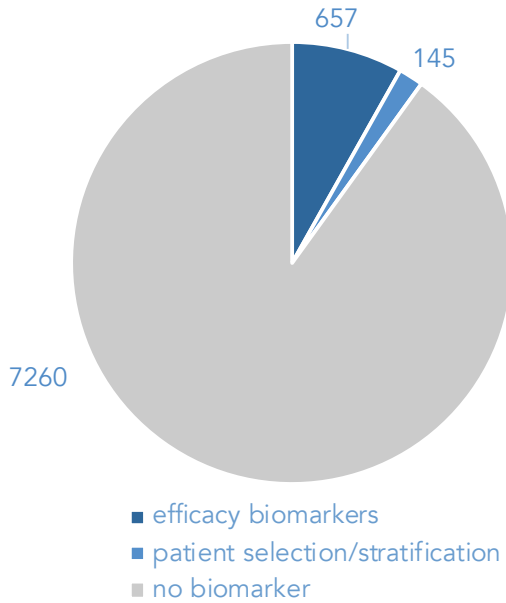
BIOMARKERS

The use of biomarkers in CNS Phase III trials is rarer than in cancer.

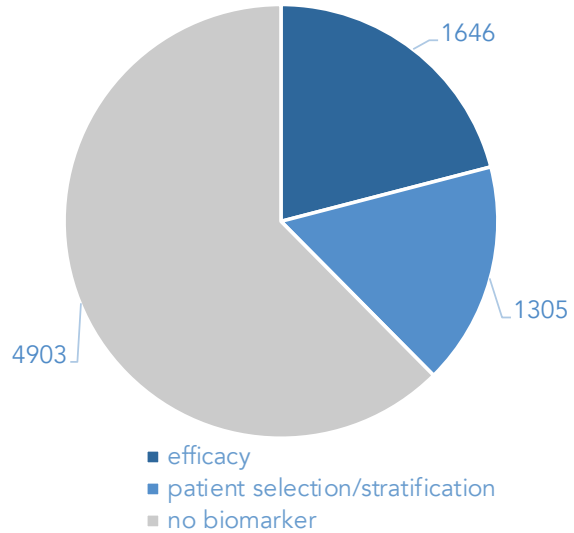
The patient selection and stratification biomarkers are particularly small in CNS trials. Some of this has to do with access to materials, as there are probably very

few brain biopsies to be utilized for brain biomarkers. Still, it's surprising how few biomarkers are being used in CNS Phase III trials.

Biomarkers in Phase 3 CNS trials



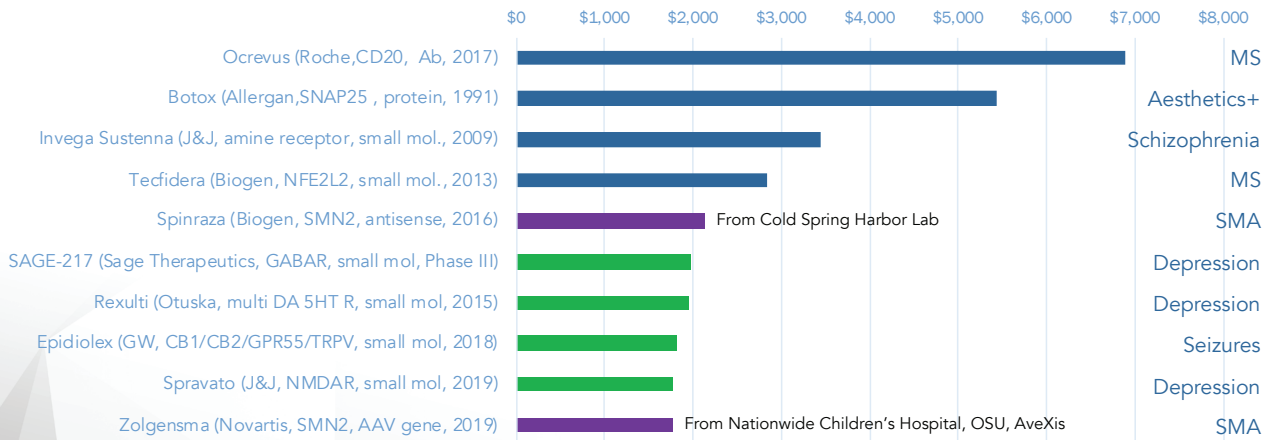
Biomarkers in Cancer Phase 3 trials



2025 SALES FORECAST

Sales for the top 10 molecules in 2025 is quite a different list than what we saw for 2018. Most of the molecules that were on the 2018 list are not in the 2025 forecast. However, Botox, Ocrevus (the Roche CD20 antibody), Invega, and Biogen's MS drug, Tecfidera, will still be on the list.

2025 Sales Forecast
Drug (Co, Target, Molecule Type, First Approval)

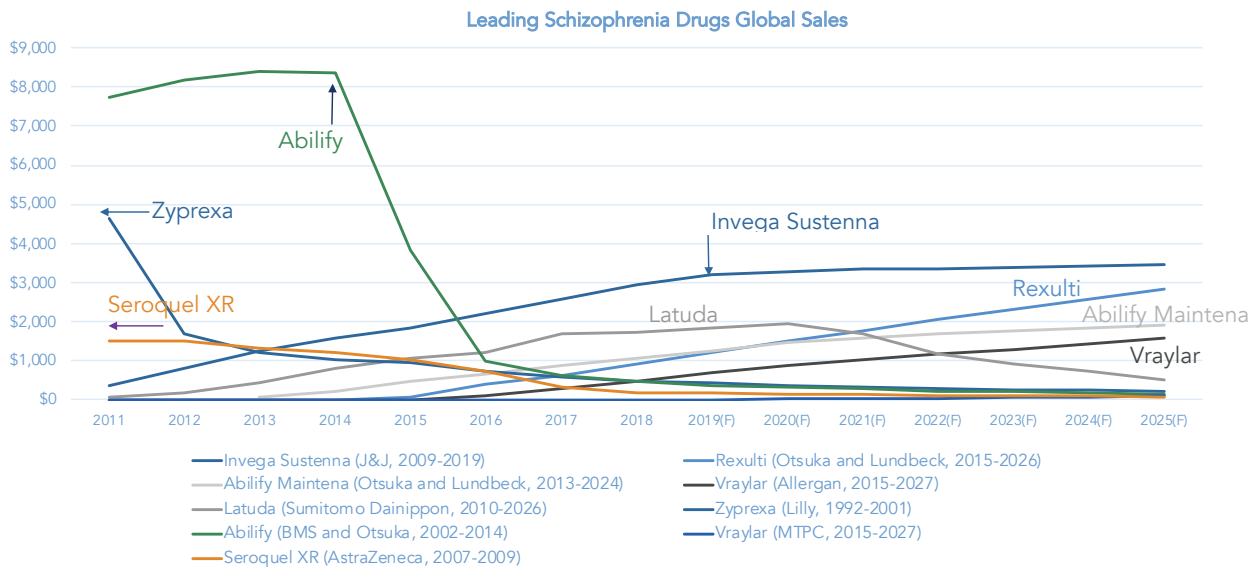


Not all the top sellers are small molecules, with antisense, gene therapy new entrants. The other big shift is that depression and seizures appear, and the list is no longer dominated by MS. The other phenomenon is that fewer of the molecules will come in via deals, which indicates that some smaller companies will be working hard to develop their own molecules and are expected to do very well.

2025 TOP 10 COMPANIES

When looking at the top 10 companies in expected sales for 2025, we will see some of the same players, such as Biogen, which tops the list. But other companies, such as Lundbeck, Teva, Merck and Lilly, are coming into play in 2025 and expected to be substantially bigger in CNS sales than they are today.

GLOBAL SALES OF LEADING SCHIZOPHRENIA DRUGS



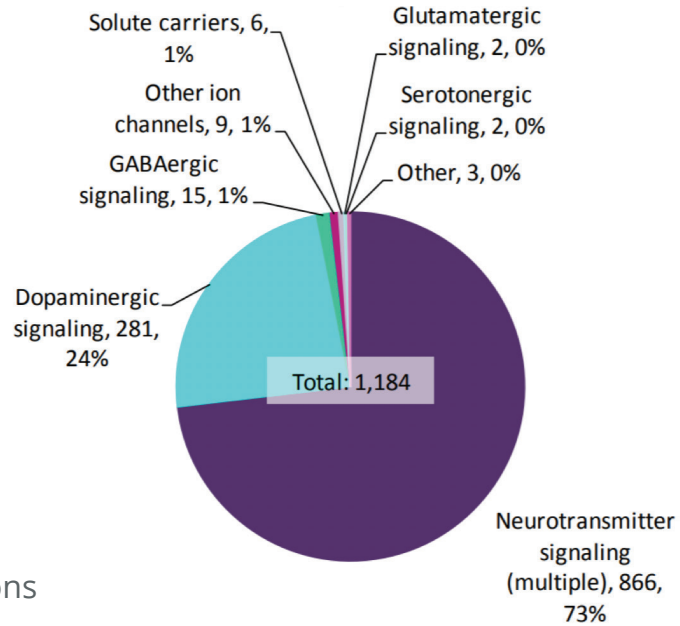
Can we add a caption to this legend Drug (Company, first approval- patent expiry)

Looking at the indication of schizophrenia, this chart demonstrates the impact on sales of patent expirations. For example, when Abilify went generic in 2014, sales dropped drastically. (arrow)

Though some drugs are forecast to have an increase in sales, these increases will not reach the levels of the large sales in the past for schizophrenia. Because the generic price pressures will be so substantial, the new drugs will not achieve the sales that were realized in the past. Despite the huge unmet needs, without new mechanisms, large sales are not forecast for schizophrenia. the huge sales of the past

MECHANISMS

One reason that this segment will not have sufficient sales to make up for losses due to patent expirations is that there are few new mechanisms. We're seeing the same mechanisms that have been used for a long time, such as dopaminergic and other neural transmitter signaling. Since they are not novel, it's hard to achieve blockbuster sales in the face of patent expirations on the old schizophrenia drugs.

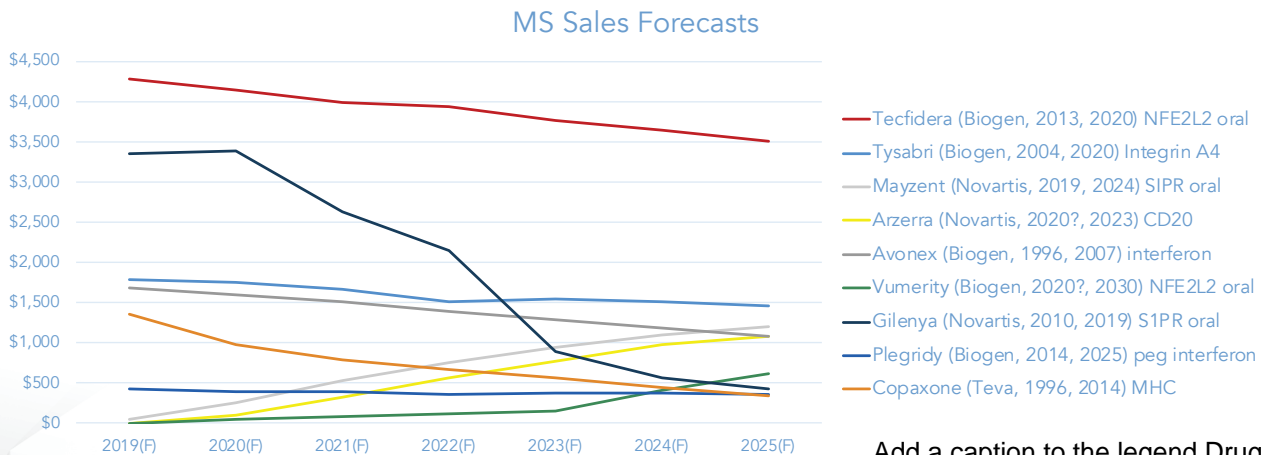


Source: GlobalData, Proprietary Marketed Products Database

SCHIZOPHRENIA'S UNMET NEEDS

There are still many unmet medical needs in schizophrenia. The existing drugs are predominantly effective on the positive symptoms, such as acting out, but also result in a dampening of effect. They don't address the negative symptoms and other side effects that patients complain about, such as cognitive impairment. Often this results in problems with patient compliance, ~~xxxxx~~ highlighting the urgent need for new approaches to treat schizophrenia.

MS SALES FORECASTS

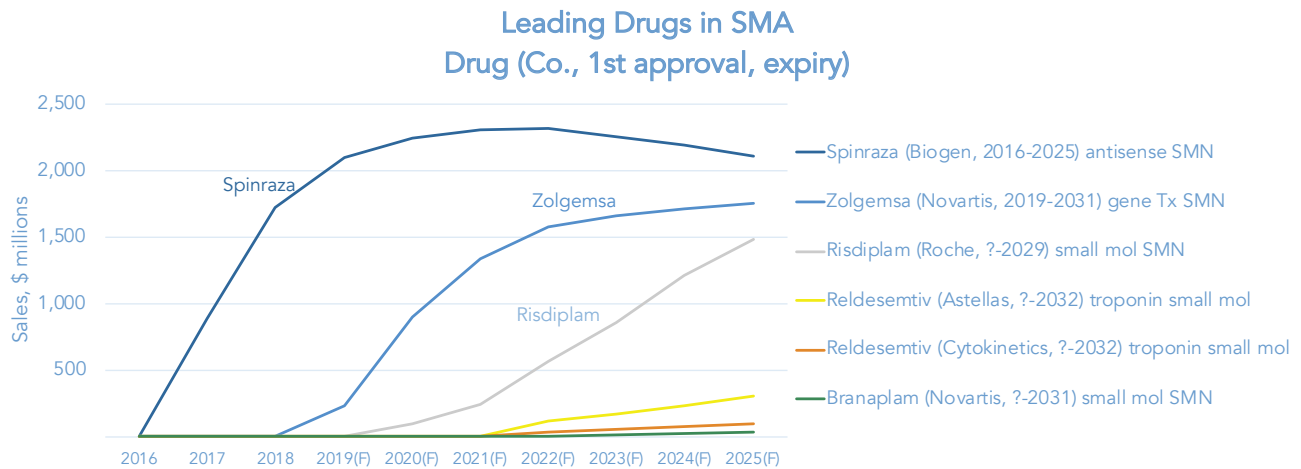


Add a caption to the legend Drug (Company, first approval, patent expiry), mechanism

In 2018, MS was the dominant indication for the top 10 drugs. Seven years later, MS is not nearly as dominant in the top 10 drugs. Again, ^{forecast as} future patent expirations and the generic price pressures will really impact MS drug sales. We have yet to see the next wave of therapeutics that differ sufficiently from the targeted immunosuppressants to make an impact in sales.

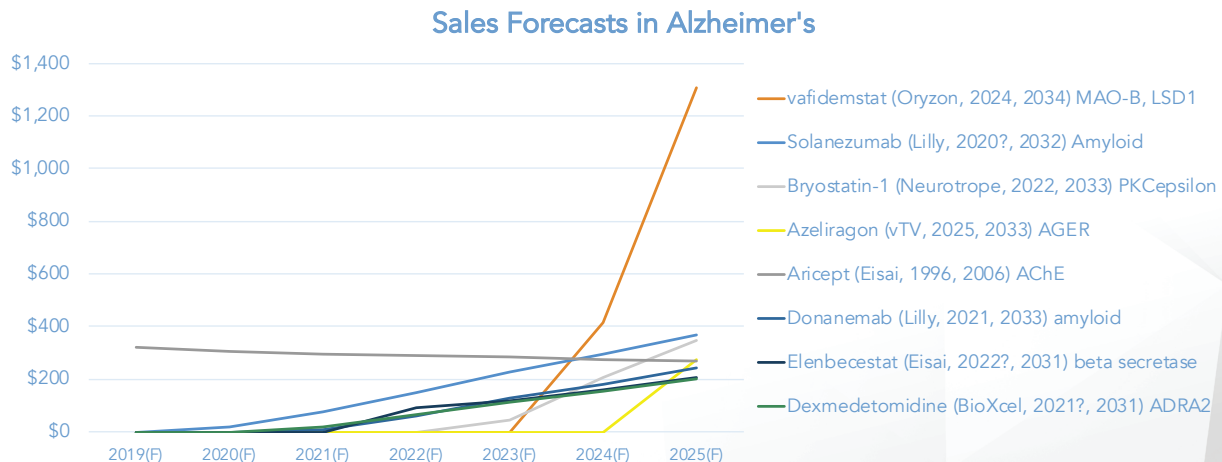
SMA SALES FORECASTS

In SMA, we see a rapid rise in sales for first entrants. This is a classic example of the power of being the first to enter a new market space. With SMA, there have been six entrants into a disease that previously had no effective treatments. We therefore see a rapid increase in sales in the early years and then a gradual slowing.



ALZHEIMER'S SALES FORECASTS

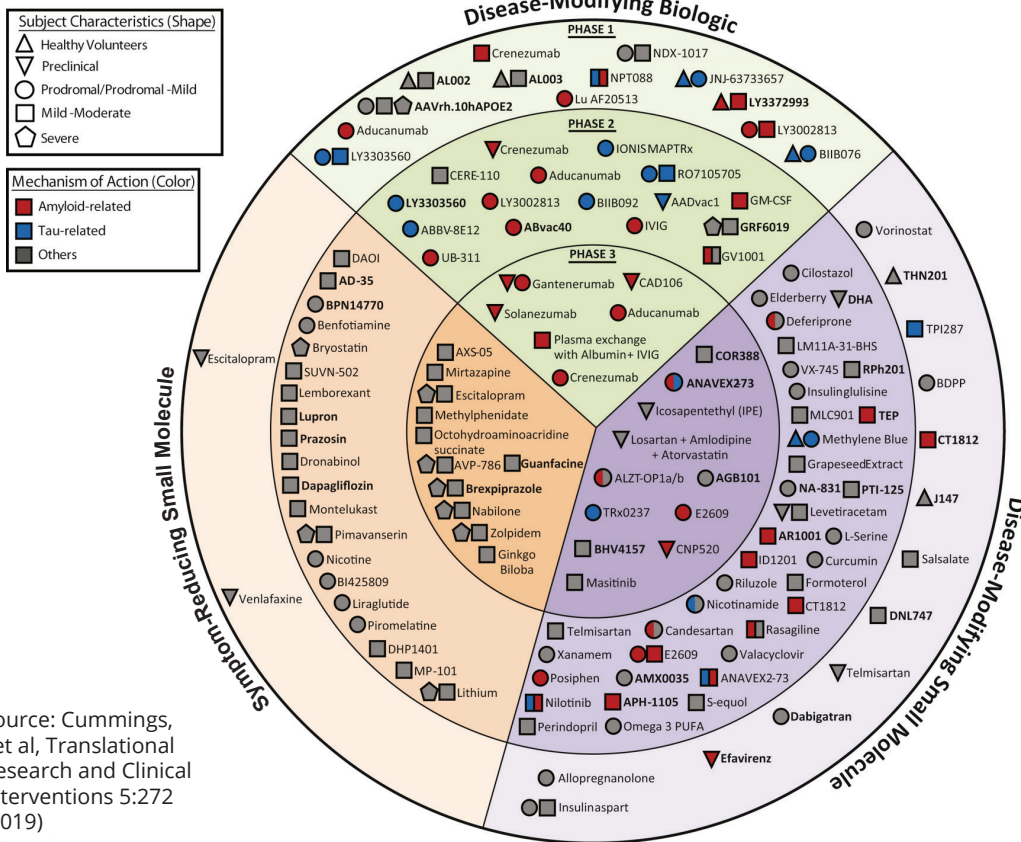
Alzheimer's has proven to be a very tough therapeutic area. Aricept was approved in 1996, and the patent expired in 2006. This acetylcholinesterase inhibitor has hung in there for a long, long time. It has benefits for some patients, but certainly can't be said to be a significant cure.



Alzheimer's sales remain fairly stagnant and analyst forecasts are generally not optimistic. The one drug showing substantial sales in the 2025 time frame is an epigenetics and MAOB approach. This is a disease with a huge unmet need, and there isn't much on the horizon that has the potential to be a blockbuster. Again, we need new approaches.

2019 DRUG DEVELOPMENT PIPELINE

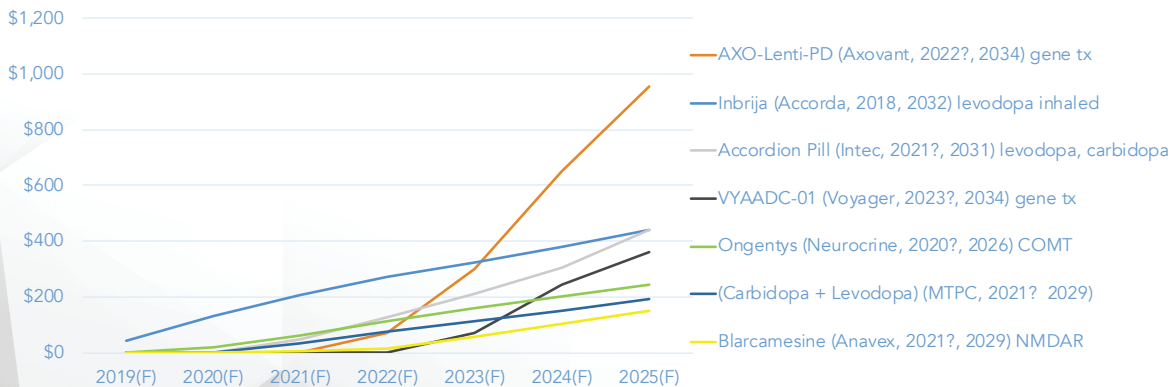
2019 Alzheimer's Drug Development Pipeline



Source: Cummings, J et al, Translational Research and Clinical Interventions 5:272 (2019)

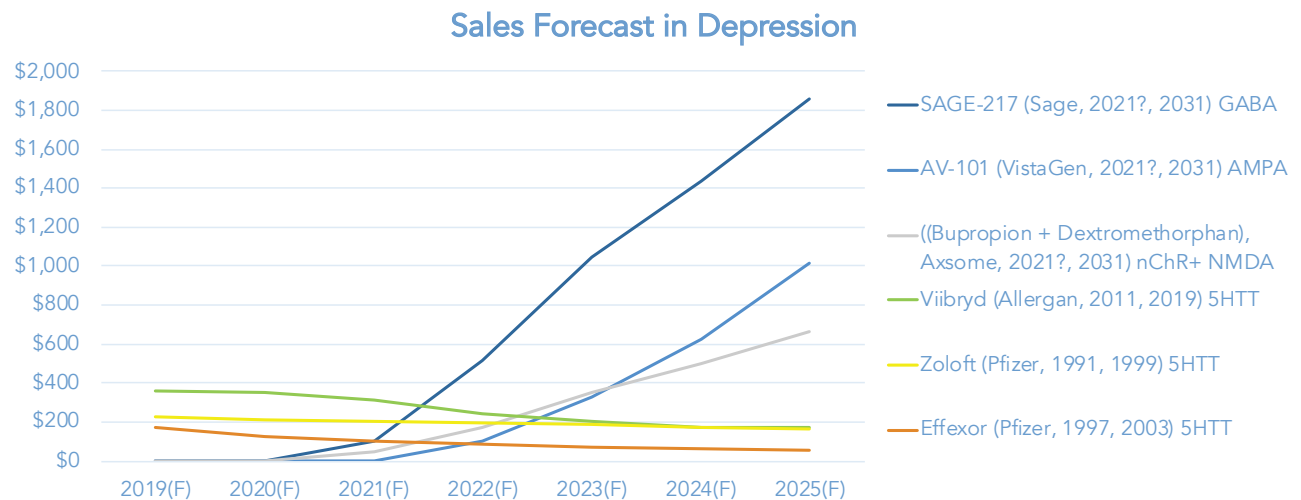
PARKINSON'S SALES FORECASTS

Parkinson's Sales Forecasts



In Parkinson's we also see that fairly stagnant growth is expected, but we do see that gene therapy has the potential to be a significant player in the future. Most of the other drugs on this list are well-known mechanisms and combinations, that is, drugs that may see incremental improvement, but are not expected to gain blockbuster status. It's difficult to get to those blockbuster sales forecasts with things that are only incrementally superior to generics.

DEPRESSION SALES FORECASTS

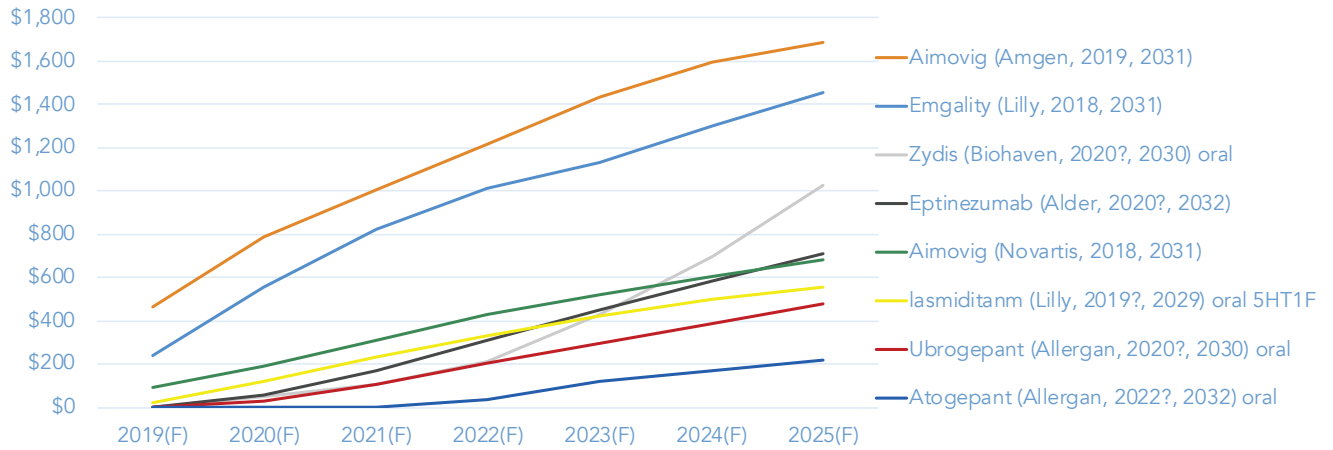


In depression, most of the serotonergic transport inhibitors have been generic for some time. They continue to have decent sales, but nowhere near the sales of the past. Dollar volume has declined dramatically, but patient volume has not been responsible. A few new approaches may have some impact, such as those employing GABAA, AMPA, and the NMDA receptor. Though Esketamine had generated tremendous hope, so far it hasn't delivered significant sales, since its benefit of the more rapid effect has the trade-off of side effects.

MIGRAINE SALES FORECASTS

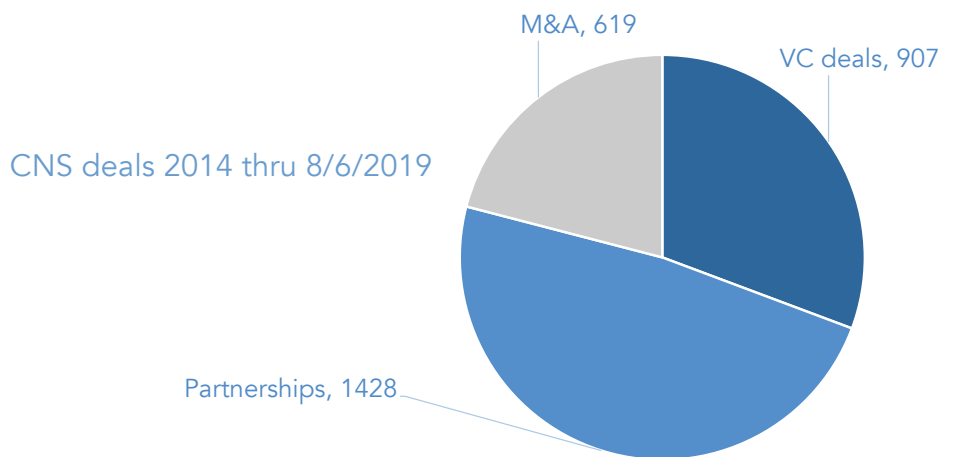
Migraine, much like SMA, is an area where the world has changed. Prior to 2019, we saw the expiration of almost all of the triptans—Sumatriptan, Zomig, Maxalt, and so forth, which had been a huge revolution at their release and represented the dominant sales in migraine. Now the CGRP agonists, mostly antibodies, have been selling well, and some oral CGRP molecules have potential. And there is one 5HT1F molecule in the list from Lilly.

Migraine Sales Forecasts

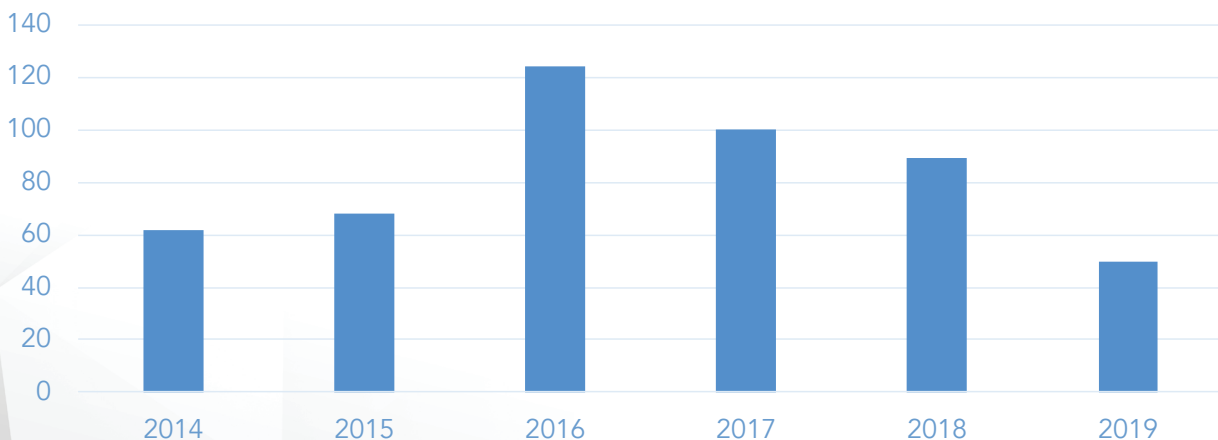


THE DEALS

This chart, which shows the fraction of deals that are M&A, VC deals, and partnerships, is consistent with other therapeutic areas, in that licensing partnerships are the predominant form of deals and is a much larger share than the number of VC deals or the number of M&A deals.



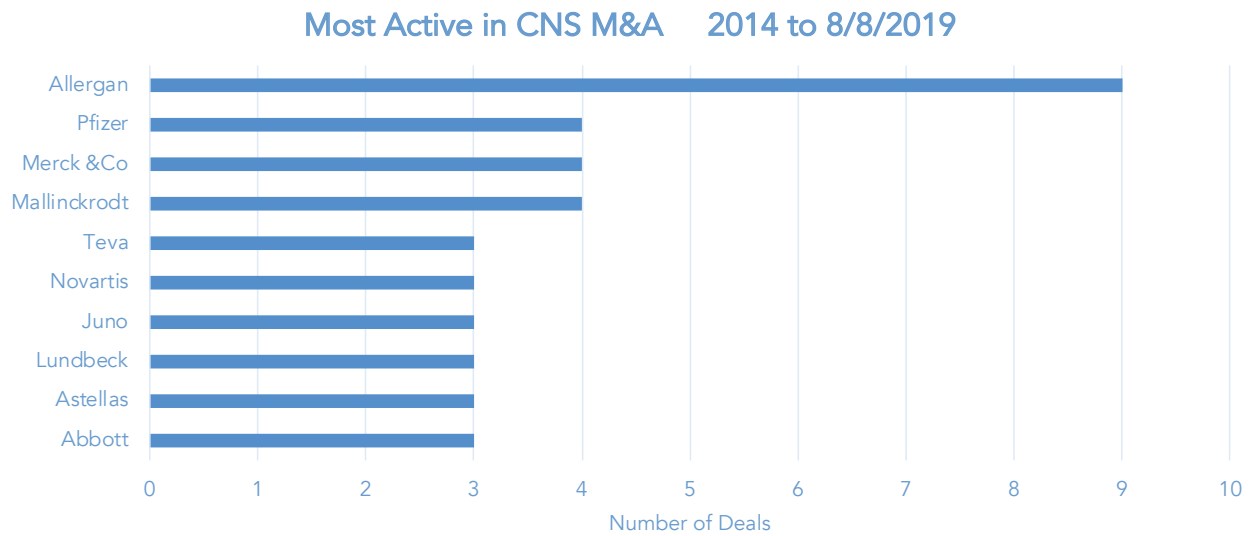
Number of M&A Deals per Year



CNS M&A DEALS

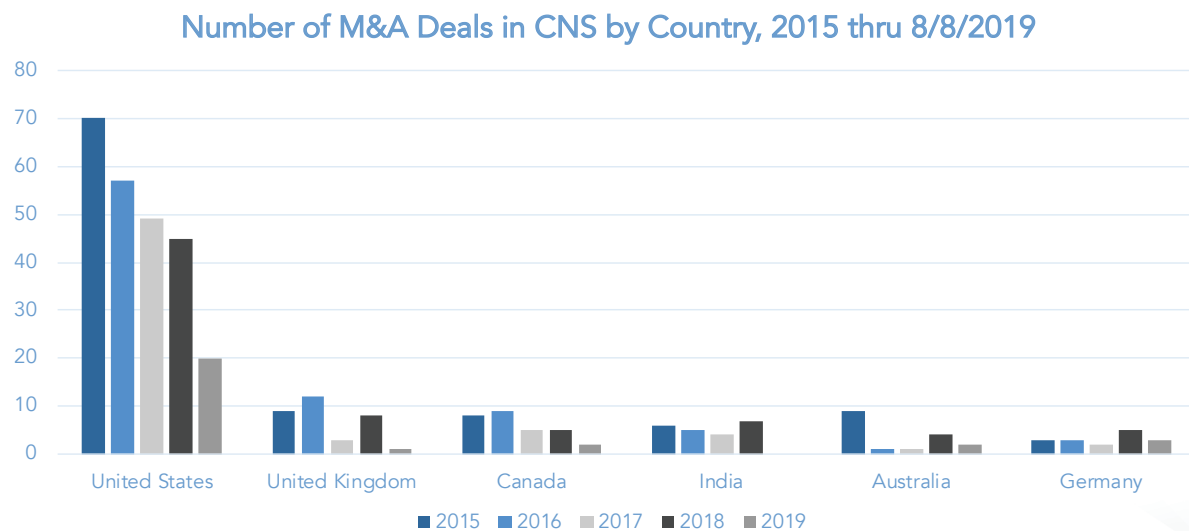
2019 is shaping up to be a strong year for M&A, but will likely not compete with 2016, when M&A deals in CNS peaked. The number of deals in CNS per year is relatively small, generally between 60 and 100 per year.

MOST ACTIVE COMPANIES IN CNS M&A



This chart shows the top companies that are doing M&A deals in CNS.

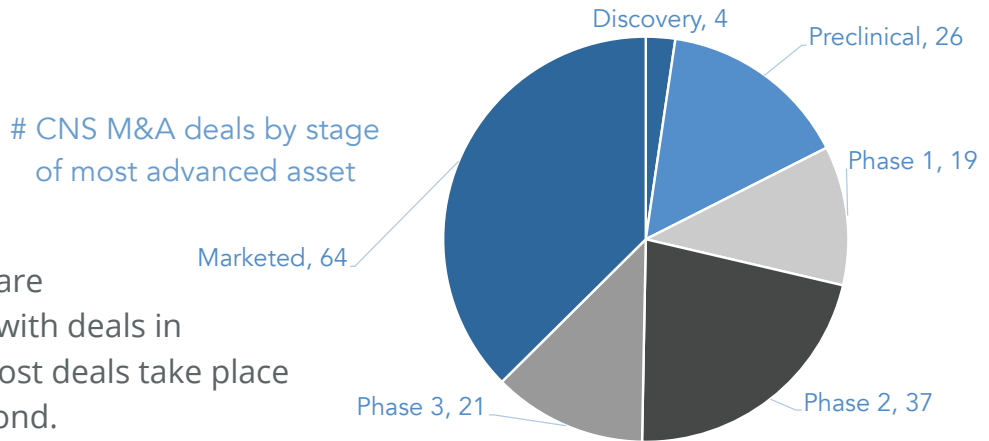
NUMBER OF M&A DEALS IN CNS BY COUNTRY



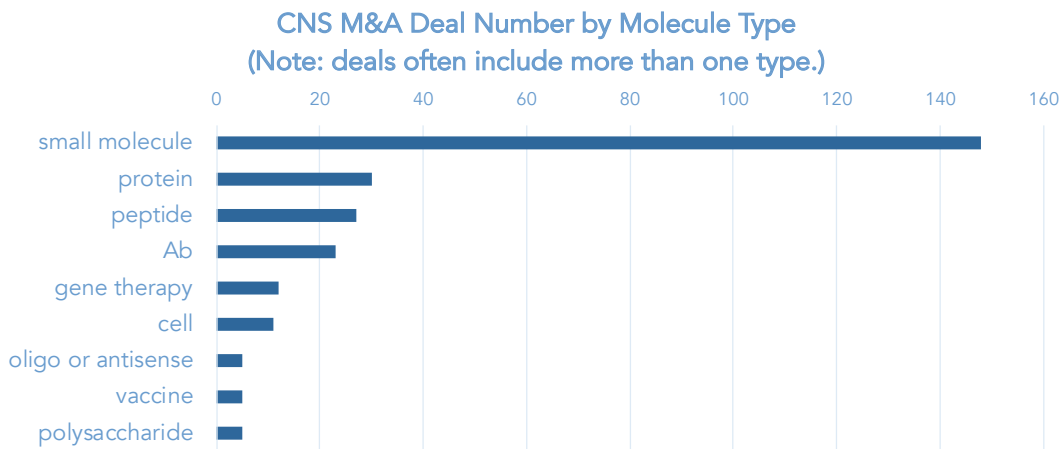
Most CNS acquisitions are for US companies. Note that China is not on this list, which differs from oncology, where China is responsible for a slightly larger number of the M&A deals.

CNS M&A DEALS BY STAGE OF MOST ADVANCED ASSET

Compared to cancer, marketed drugs are more prevalent in M&A deals in CNS, but a significant number of preclinical deals are taking place, along with deals in Phase I, II and III. Most deals take place at Phase II and beyond.



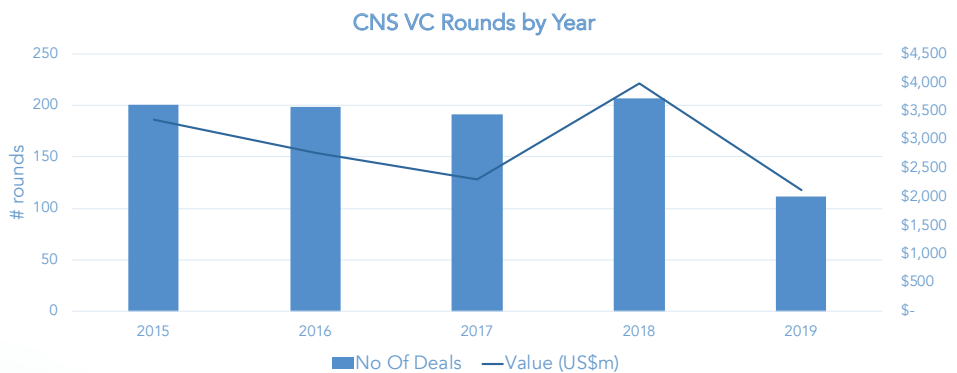
CNS M&A DEALS BY MOLECULE TYPE



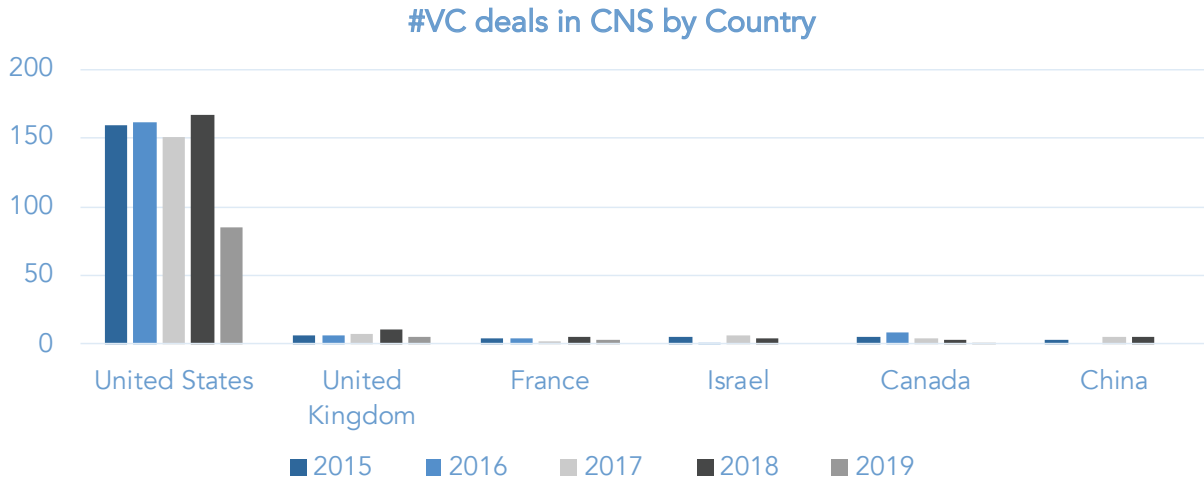
Small molecules dominate M&A deals in CNS, but these deals are getting done across a wide variety of types of molecules.

VC DEALS

The number of VC rounds per year in CNS has been generally steady for the last five years, and the number of VC deals and the deal value in 2019 are on track with the previous four years.



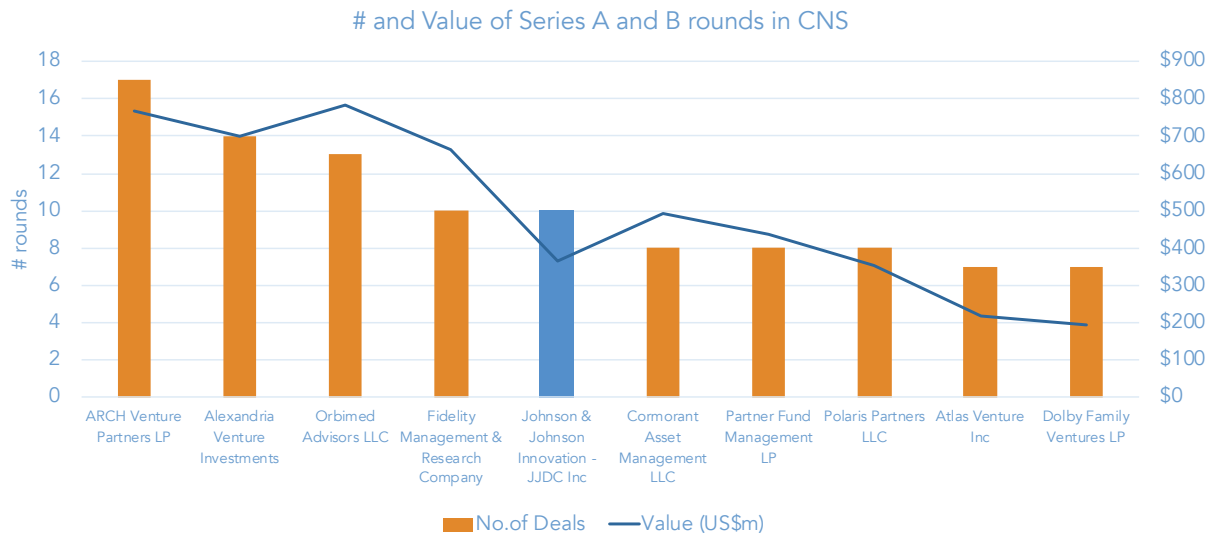
NUMBER OF VC DEALS IN CNS BY COUNTRY



Vcs are really rarely funding CNS companies outside the United States.

NUMBER AND VALUE OF SERIES A AND B ROUNDS IN CNS

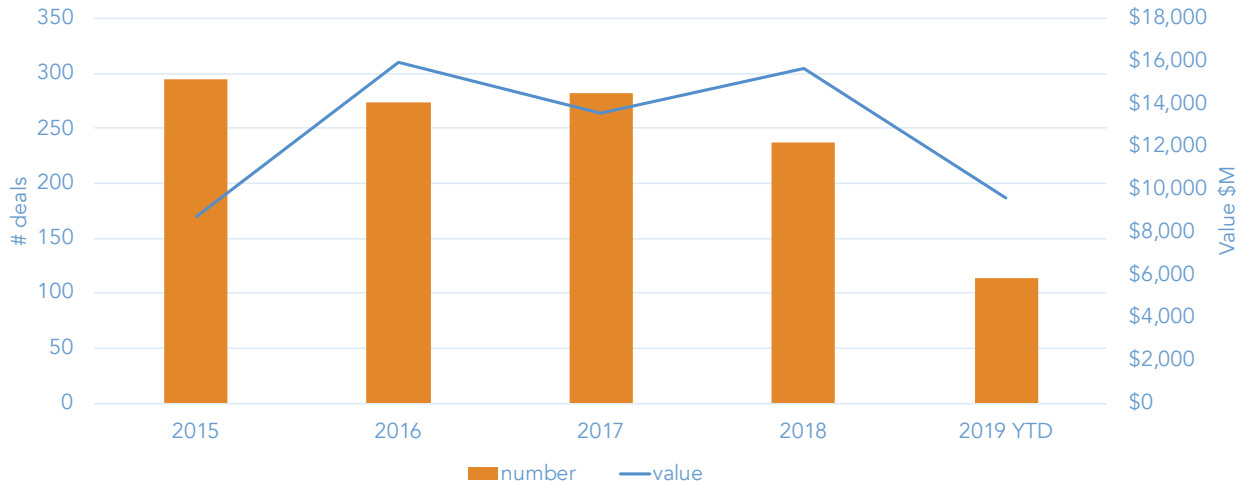
Who's doing Series A and B round in CNS? This area looks quite different from oncology, a field where a number of corporate venture arms are among the most active in early round deals. Instead, in CNS, the players who have been the most active in series A and B rounds includes only one corporate VC.



LICENSING DEALS

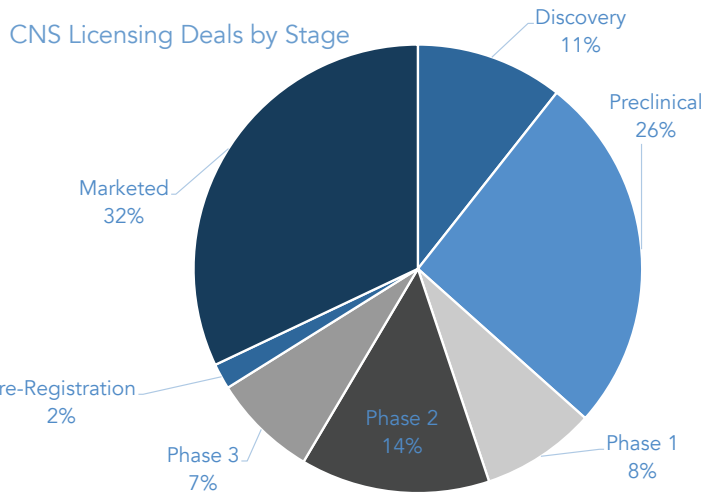
CNS licensing deals have been steady in recent years, both in number and value, and 2019 looks to be no different. Note (on the next page) that there are many more deals here in licensing than in M&A and VC.

CNS Licensing Deals since 1/2015



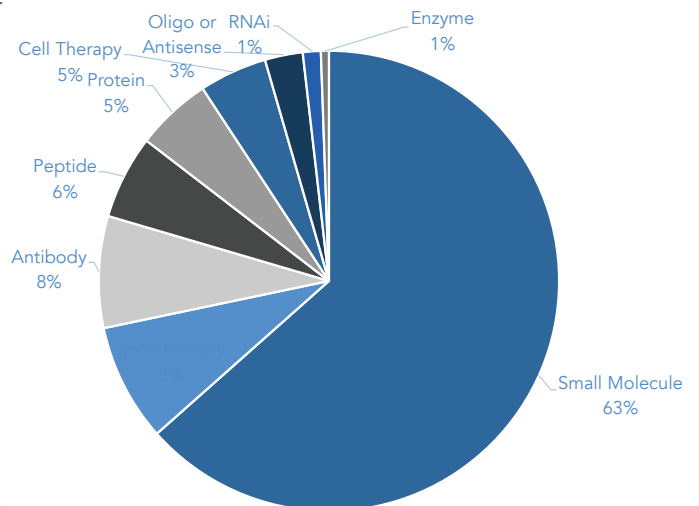
CNS LICENSING DEALS BY STAGE

CNS licensing deals are most often done in the preclinical and marketed stages. This is somewhat different than in oncology, where the percentage for marketed drugs is much smaller. The preclinical percentage is similar to oncology, and the Phase II percentage is a bit smaller than in oncology, but the basic message is the same—most deals are done in preclinical, Phase II, and beyond. Phase I is a tougher arena for deals. Phase III is also often a tougher arena because companies need lead time to be ready to launch, and often the best opportunities are perceived to have been picked up in Phase II when there are signs of efficacy, but everything’s still not complete.

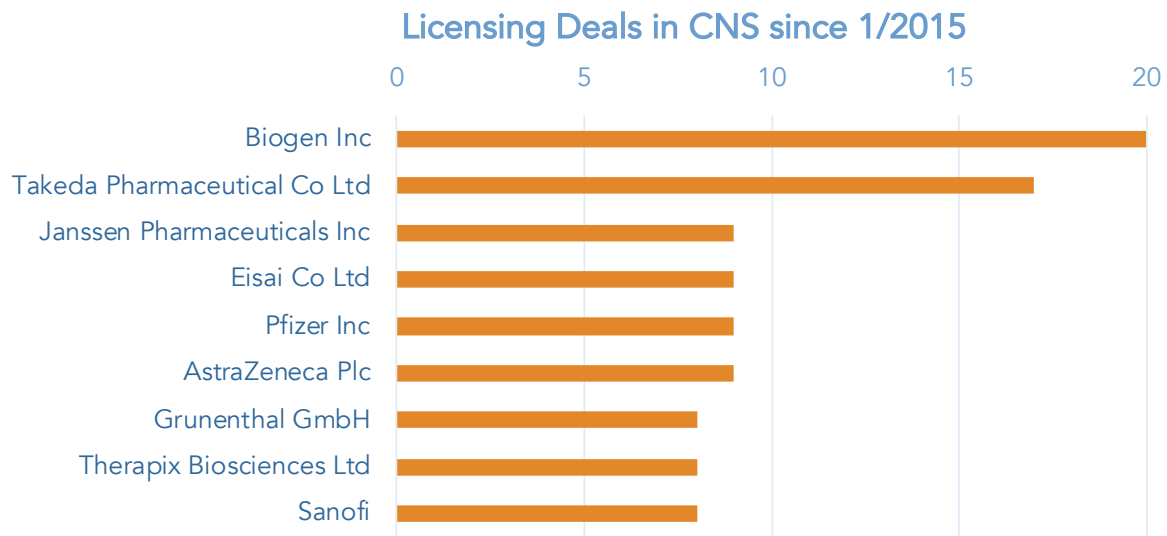


COMMON MOLECULE TYPES IN CNS LICENSING

Small molecules own the dominant share of CNS licensing deals, but there are a significant variety of other molecule types, which could reflect a desire for diversification of platforms.



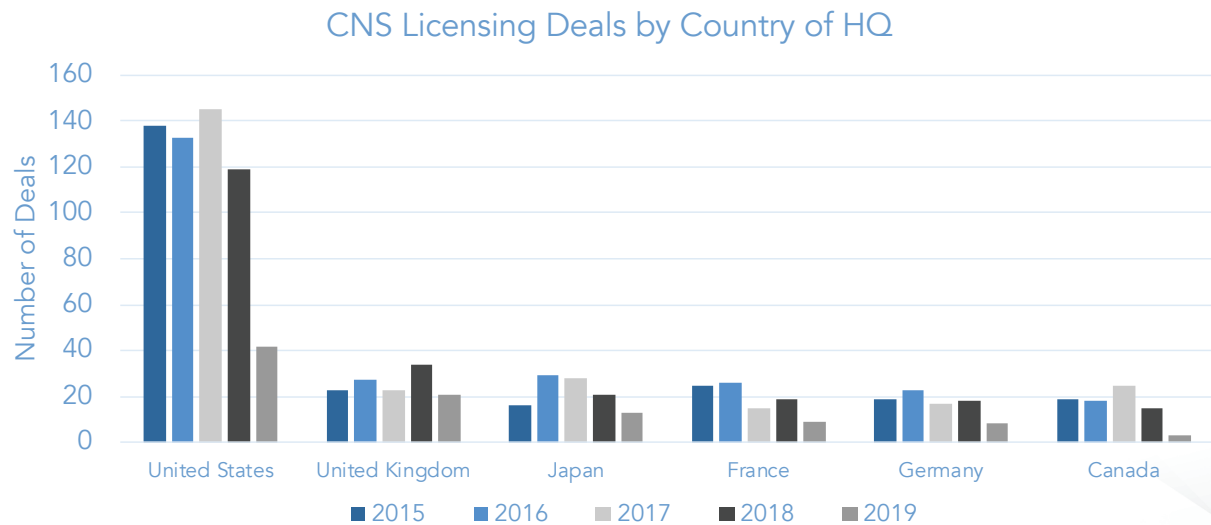
LICENSING DEALS IN CNS SINCE JANUARY 2015



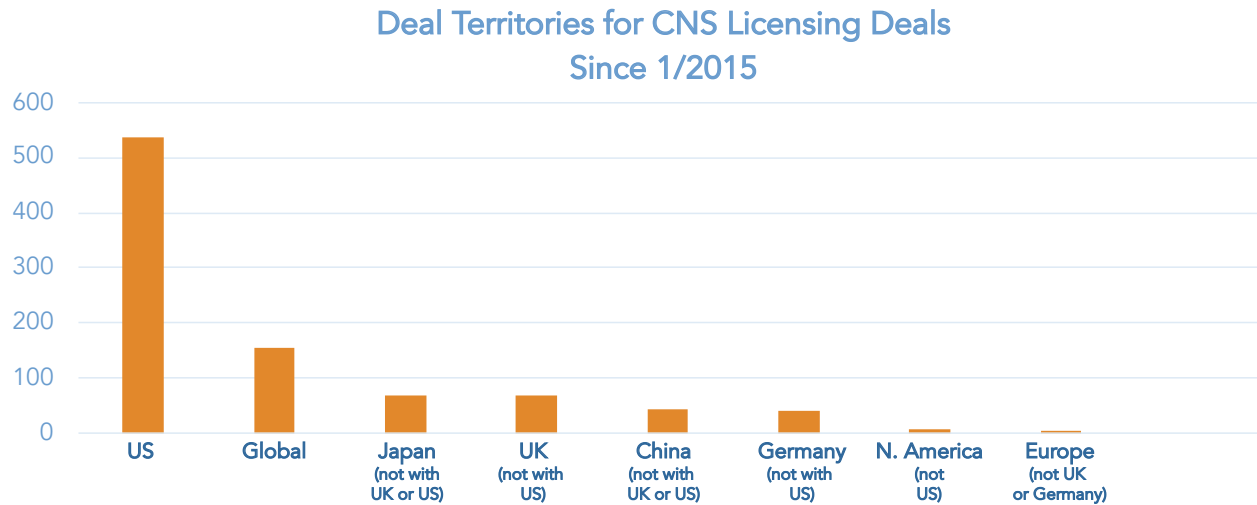
Biogen and Takeda have been the most active in-licensors in the last five years, but it's notable that Biogen has only done about five deals a year. Therefore, if you're looking for a partner, you might not be able to count on even a big dealmaker like Biogen.

CNS LICENSING DEALS BY COUNTRY AND TERRITORY

US companies are the most active in doing licensing deals in CNS.



Licensing deals in CNS generally include the US even if they are not global. This is consistent with the US having the biggest sales in CNS drugs.



and

In summary, with tremendous unmet needs, large patient populations, CNS is a potentially exciting area.

But many diseases show pricing pressure of generics against the incremental improvements. With new approaches, new unserved diseases, the future is likely to be very different.

About Linda Pullan, PhD

Pullan Consulting

Linda and her team at Pullan Consulting offer biotech and pharmaceutical companies consulting in all aspects of partnering. Linda has a PhD in Biochemistry, a BS in Chemistry, and over twenty years of drug industry experience, including work on more than 75 deals.



About Pullan Consulting

STRATEGY

Pullan Consulting can help you decide which studies will be more important for a partner or an investor. They can also help assess partnerability of new indications or programs.

OUTREACH

Pullan Consulting can mount an email partnering campaign, represent you at partnering meetings, and introduce you to investors. They have a very large database of industry contacts, along with notes on their interests, and they subscribe to databases to facilitate searches for companies in your space.

EVALUATIONS AND VALUATIONS

Pullan Consulting can assess differentiation from competition, both existing and in the pipeline. They can also model risk-adjusted discounted cash flow value of your drug candidate or of a deal.

NEGOTIATIONS

Pullan Consulting can help you prepare for a deal, both by considering the alternatives of deals and by evaluating your priorities. They can also lead negotiations for you or give advice on how to negotiate.



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