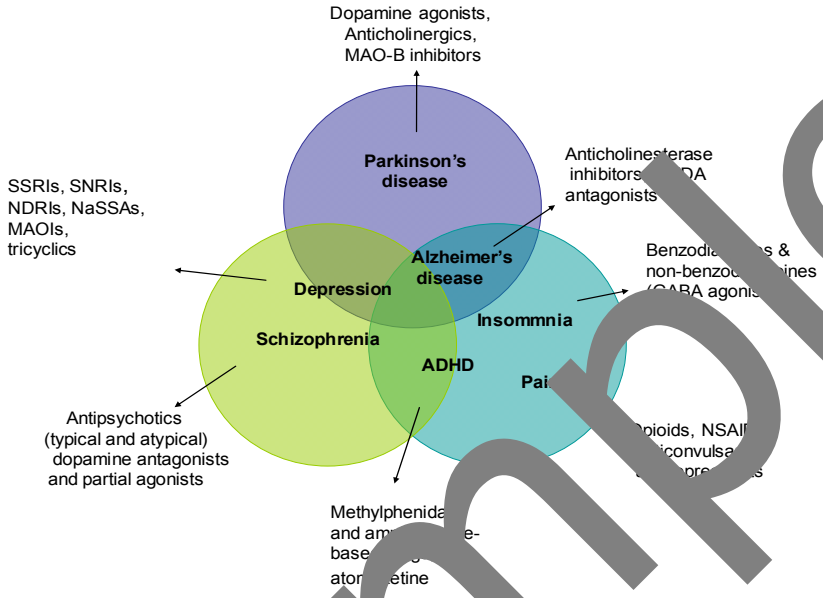
1.2 Current CNS therapies

CNS sales incorporates a wide range of therapeutic areas ranging from neurodegenerative disorders such as Alzheimer's disease and Multiple Sclerosis to anxiety/depression, insomnia and pain (see Figure 1.4). Several drug classes may be used to treat a cross-section of CNS conditions, for example, antipsychotics may be used to treat schizophrenia, depression and pain.

Figure 1.4: Classes of CNS drugs approved



Source: Pharmavision.co.uk

1.2.1 P[illegible]ct drivers [illegible]d da[illegible]peners

CNS g[illegible]al sales were driven [illegible]a num[illegible]r of factors which were dependent on the specific disorder treated[illegible] number [illegible] in[illegible] CNS global sales, according to the particular disorder:

- The neurodegenera[illegible]e market (Alzheimer's disease, multiple sclerosis, Parkinson's disease) has seen several new d[illegible]gs launched, generic reformulations and new drug candidates in development;
- The rise i[illegible]eric markets, with reformulations such as extended release, oral melt and transdermal, particularly for pain, antipsychotics, antidepressants and sleep disorders;
- Extended licenses for existing products, particularly in psychiatry, with antipsychoatic drugs gaining licenses to treat affective disorders (bipolar disorder, depression) and anxiety;
- Availability of new drugs with a lower propensity to induce dependence in anxiety disorders and insomnia, such as non-benzodiazepine hypnotics and anxiolytics ;
- Changes in the structure of the health system leading more "specialist" CNS drugs to be prescribed in Primary Care settings;

		intracranial cather	
National Science Institute (US) In collaboration with Vanderbilt University	Nanosponge	Non-invasive	Under a 5 year grant obtained from NSI October 2007 NSI is developing a nanoparticle with extensive internal cross-linking to compress a long, linear molecule into a sphere about 10 nm diameter sphere (about the size of a protein). It is able to carry large numbers of drug molecules to target cells, can pass through the BBB and has been manipulated to target drug delivery to tumours in the lung, brain and spinal cord
NeuroGeneration	Neural stem cell therapies, Parkinson's disease (dopamine producing stem cells) Stem cell therapy	Stem cell implantation & Cellular reprogramming with DNA-methy and manip ation of transcr nal factors, itu neurogenes nd co-neuro omics human l stem cell lines.	The Com y is col ing on se al produ in clini velopm th: UCLA B Research Institute, Ceda Sinai Medical Center, University of Milan, niversity of Tallin, Estonia; urrently seeking investors and further collaborations Phase II clinical trials for Parkinson's disease
Neurobiological Technologies Inc /Celtic Pharma	Synthetic r uration of a natura man peptide (C ophin eleasi ctor)	cutaneous inj ion	Development of Xerecept, cortiorelian acetate injection for peritumoural cerebral oedema
Northwest Biothera ics	DC-V va e for brai ancer	Injectable	DC-vax commercially available September 2007
Penwe	Per est's TIM (r)	Oral	Development of Opana ER, oxymorphone hydrochloride extended-release tablets technology and is indicated for the treatment of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Marketed by Endo Pharmaceutcials Ltd
Perfusion Technology LCC	Ultrasound device for opening the BBB	Delivered by placing the device on the head while drug treatment is in progress	Pre-clinical studies, human studies to commence in 2008
Repligen	Uridine is a biological compound essential for the synthesis of DNA and RNA Uridine is synthesized by the	Oral	RG2417 Uridine (bipolar disorder (Phase II), neurodegeneration (preclinical)

6.3 Our opinion on minimally invasive delivery

Where the technology is now, its evolution, achievements and pitfalls

Our definition of minimally invasive delivery technologies are those treatments targeted for CNS delivery that do not directly impinge on brain/CNS tissue, but require some invasion, i.e. injectable technology, or systemic implantable technology; "opening" of the skin to allow the active pharmaceutical ingredient (API) to be clinically effective. Intrathecal drug delivery has been used mainly to deliver high potency drugs for anti-cancer therapy, or intractable pain: this delivery method may become obsolete as novel, non-invasive ways of opening the BBB are approved.

Competition

Competition in this market is limited and has attracted the attention of some smaller "start-up" players. For example, Ekos is well positioned with its intra-arterial/IV + ultrasound catheter for ischemic stroke impact. Implantable technologies such as those from ALZA, continue to have considerable promise, as drug d[illegible] can be controlled remotely, and take place for up to a year in some cases after the one invasive implanta[illegible] even[illegible] onversely, convection enhanced delivery whilst interesting is not widely used and is indicated o[illegible] for sp[illegible]ic cases, therefore, is unlikely to ever make a big impression on the delivery market.

Potential future applications

We anticipate CNS implants will have a major role to play in the futu[illegible] deliv[illegible] particularly with the development of biocompatible/biodegradable materials whereby sy[illegible]mic imp[illegible]s can [illegible] be engineered to deliver a variety of molecules over various periods of time. The advant[illegible] of implants [illegible] that they are an effortless method of drug delivery for the patient; also some implants can be [illegible]motely" co[illegible]olled by the treating physician.

Activity in the market

Medtronic continues to be active and clinical tria[illegible] combining [illegible]ogen/e[illegible]ical stimulation therapy for the treatment of brain injuries looks promising. Im[illegible]ntab[illegible]chnology is growing[illegible]eld, and the demand for more long-term delivery systems that reduce dosi[illegible]urden and[illegible]sure compliance is high. As delivery technology becomes more refined and implant doses can[illegible] controlled r[illegible]otely, CNS treatments may re-evaluated, especially those that were previously delivered by alternat[illegible]ethods with[illegible]ow patient compliance.

Major players

Medtronic is a m[illegible] player in this fi[illegible] but ne[illegible]aller players are emerging. Ekos may find a foothold in the market with its [illegible]omising catheter/u[illegible] sound [illegible]stem for ischemic stroke whilst Pefusion Technology's ultrasonic device shows [illegible]tential, but m[illegible] inf[illegible]tio[illegible] needed on both these technologies before their full potential can be assessed.

Winners

We believe Medtronic wil[illegible]ue to be a market leader, due partly to their reputation as an innovator of effective delivery devices, and their broad and deep product portfolio. Medtronic also has a track record of effectively treating CNS disorders, particularly those conditions such as chronic, intractable pain, which have proved an unmet challenge so far for other drug delivery companies.

7.3 Intranasal/pulmonary delivery

Once relegated to treating conditions such as nasal congestion and rhinitis, intranasal drug delivery is now gaining attention for administration of a wide range of pharmaceuticals. Advantages of intranasal drug delivery include:

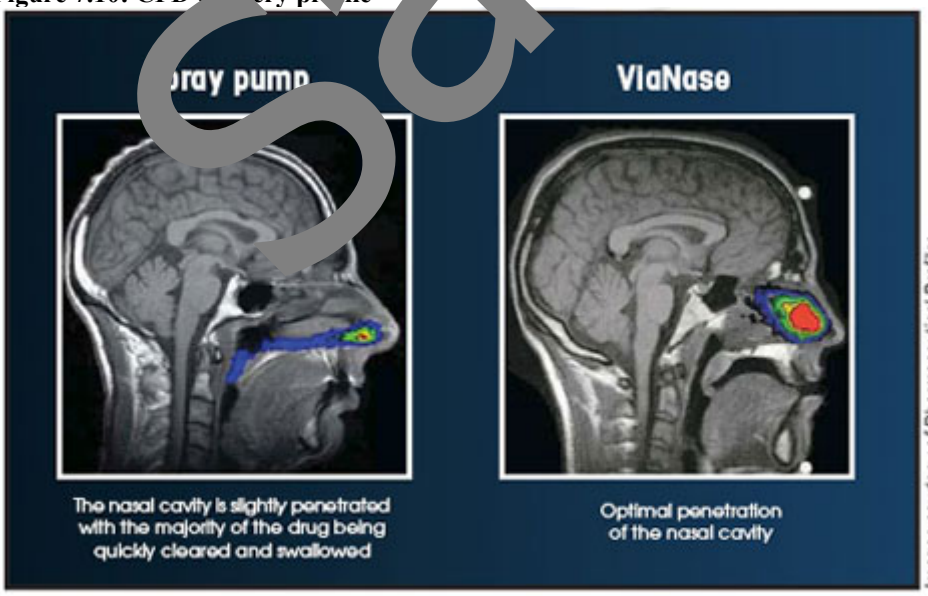
- Avoidance of the gastrointestinal tract and first-pass metabolism
- Large nasal musocal surface area for dose absorption
- Rapid drug absorption via highly vascular nasal mucosa
- Rapid onset of action
- Non-invasive, easy to administer
- Improved bioavailability
- Lower dose/reduced side effects
- Minimal aftertaste
- Improved convenience and compliance
- Self-administration
- New patent coverage for drug formulations about to expire.

7.3.1 Case study: ViaNase - Controlled Particle Dispersion (Kurve Technology)

Kurve Technology has developed its proprietary Controlled Particle Dispersion (CPD) versatile device technology platform for the intranasal delivery of a wide range of topical, systemic and nose-to-brain medical therapies. The device is a pocket-sized, hand-held spray that uses a patented principle of vortical flow, effectively disrupting inherent nasal cavity airflows to deliver drug formulations to the entire nasal cavity, the olfactory region, and the paranasal sinuses.

Preliminary studies suggest that CPD may lead to more effective intranasal delivery of small molecules compared to nasal spray bottles that deliver formulations only as far as the anterior portion of the nasal cavity (Figure 7.10). In addition, the enhanced ViaNase "Intelligent Device" (IDD) includes extra features to aid compliance and ensure correct dosing of the drug, and prevent drugs being given past their expiration date. It can also be programmed to the individual patient's specifications, taking into account parameters such as optimized droplet size, atomization rate, vortex characteristics and breath actuation.

Figure 7.10: CPD delivery profile



Technesium MRI studies comparing formulation delivery with spray pump vs. ViaNase

Source: Kurve Technology[20]

[20] *www.Kurvetech.com/TechnologyClinical.asp*