Does Psychopharmacology Have a Future?

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Infelici e Tristi: O Malati Di Depressione?
Trieste
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An absurd question?

- PP certainly has a powerful present, as we shall see
  - The use of PP drugs is not in decline
- PP has become integral to many practices for the government of mental states and human conduct
  - It is hard to imagine a world without these drugs
- And the future looks promising
  - Many new markets to exploit in BRICS and other regions
  - Many new problems to address – dementia, Parkinsons, enhancement….
- BUT not quite the future dreamed of in the 1980s
  - The dream of precision, specificity, efficacy based on an understanding of mechanism
- So what kind of future is there for PP?
  - This will be the question for discussion today
- A new dream - personalisation via brain signatures?

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THE PSYCHOPHARMACOLOGICAL PRESENT

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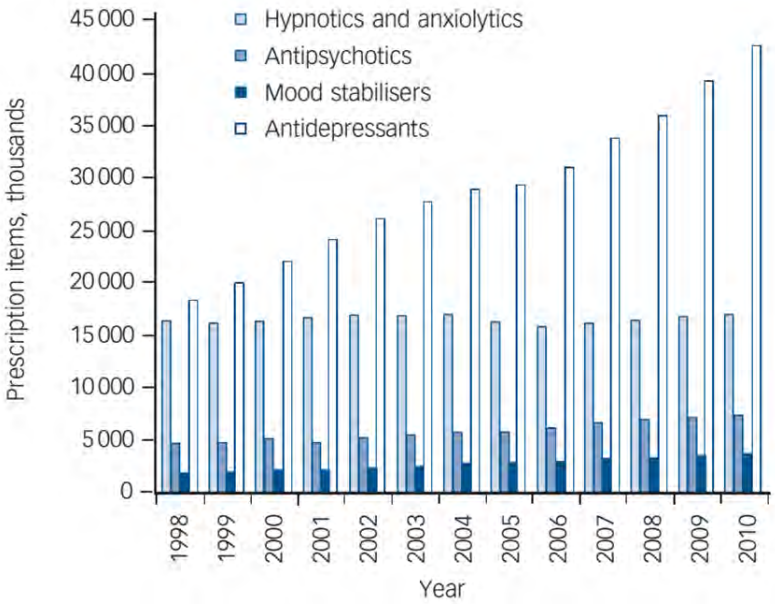
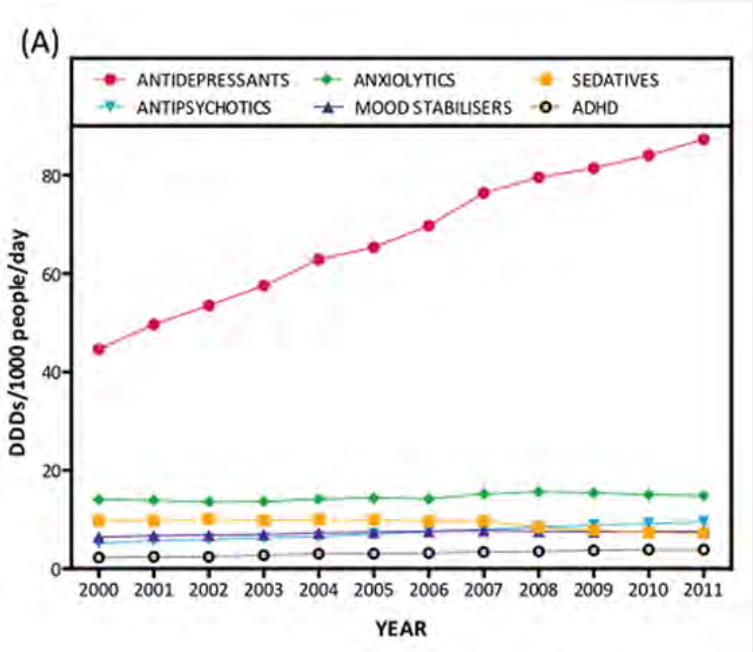
The Pharmacological Present



UK 1998-2010
(Ilyas and Moncrief 2012)



Australia 2000-2011
(Stephenson et al. 2013)

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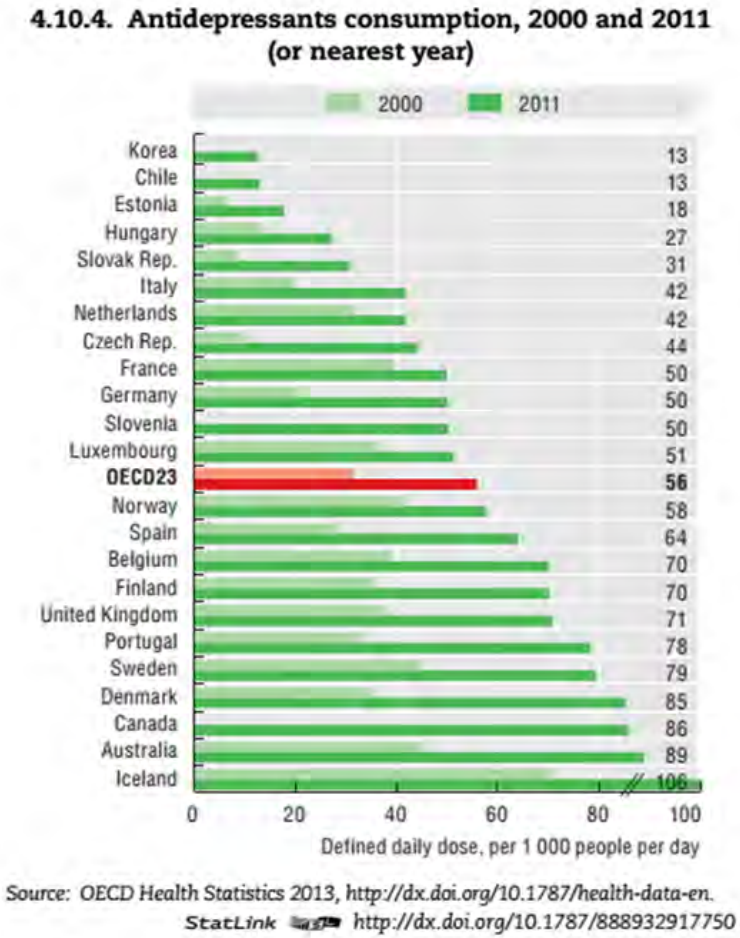
Our Depressed Present?



Antidepressant Prescribing in Spain, Germany, Denmark, UK and the Netherlands has shown an increasing trend from 2001-2009, with a higher rate for women. **(Abbing-Karahagopian et al., 2014)**

'In Italy there was a twofold increase in Antidepressant consumption between 2001 and 2007" **(Damiani et al. 2013)**

The Netherlands an increase in prescriptions of psychotropic drugs, with the exception of anxiolytic drugs from 2001-2006. **(Wittkmpf et al. 2010)**

Canada, USA, Greece and Ireland have all shown an increase from 2007-2011, in the use of antidepressants, with a noticeably higher rate in North America when compared to Greece and Ireland. **(Wilby et al. 2013)**

The use of anxiolytics has declined slightly from 1997 to 2008 in Denmark. **(Holm et al. 2012)**

In 2013 in England alone over 53 million prescriptions were issued for antidepressants, a 6% increase on the previous year and a 92% increase since 2003. **(Health and Social Care Information Centre, 2014)**

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Top 25 Psychiatric Medication Prescriptions for 2011

psychcentral.com

2011 Rank	2009 Rank	2005 Rank	**Brand name** ***(generic name)***	**Used for…**	**U.S. Prescriptions** (% change from 2009)
1.	1.	1.	Xanax *(alprazolam)*	Anxiety	47,792,000 (9%)
2.	17.	11.	Celexa *(citalopram)*	Depression, Anxiety	37,728,000 (36%)
3.	4.	2.	Zoloft *(sertraline)*	Depression, Anxiety, OCD, PTSD, PMDD	37,208,000 (8%)
4.	3.	5.	Ativan *(lorazepam)*	Anxiety, panic disorder	27,172,000 (4%)
5.	5.	4.	Prozac *(fluoxetine HCL)*	Depression, Anxiety	24,507,000 (6%)
6.	2.	3.	Lexapro *(escitalopram)*	Depression, Anxiety	23,707,000 (- 16%)
7.	6.	NA	Desyrel *(trazodone HCL)*	Depression, Anxiety	22,591,000 (15%)
8.	7.	16.	Cymbalta *(duloxetine)*	Depression, Anxiety, fibromyalgia, diabetic neuropathy	17,770,000 (6%)
9.	10.	9.	Valium *(diazepam)*	Anxiety, Panic disorder	14,694,000 (6%)
10.	8.	13.	Seroquel *(quetiapine)*	Bipolar disorder, Depression	14,213,000 (- 11%)
11.	11.	10.	Paxil (paroxetine HCL)	Depression, Anxiety, Panic disorder	13,990,000 (- 6%)
12.	9.	6.	Effexor XR (venlafaxine HCL ER)	Depression, Anxiety, Panic disorder	12,469,000 (NA for HCL ER)
13.	22.	10.	Wellbutrin XL (bupropion HCL XL)	Depression	12,151,000 (77%)
14.	12.	14.	Risperdal (risperidone)	Bipolar disorder, Schizophrenia, irritability in autism	12,092,000 (14%)
15.	11.	NA	Amphetamine salts (Generic)	Attention deficit disorder	9,682,000 (36%)
16.	15.	NA	Abilify (aripiprazole)	Bipolar disorder, Schizophrenia, Depression	8,881,000 (8%)
17.	19.	NA	Vyvanse (lisdexamfetamine)	Attention deficit disorder	8,467,000 (50%)
18.	NA	NA	Wellbutrin SR (bupropion HCL SR)	Depression	8,456,000 (75%)
19.	13.	NA	Vistaril* (hydroxyzine)	Anxiety, tension	7,268,000 (9%)
20.	NA	NA	Amphetamine salts ER (Generic)	Attention deficit disorder	6,499,000 (67%)
21.	18.	19.	Buspar (buspirone)	Sleep, Anxiety	6,334,000 (15%)
22.	20.	17.	Zyprexa (olanzapine)	Bipolar disorder, Schizophrenia	4,576,000 (- 15%)
23.	16.	NA	Concerta (methylphenidate)	Attention deficit disorder	4,328,000 (- 45%)
24.	NA	NA	Methylphenidate (generic)	Attention deficit disorder	4,248,000 (NA)
25.	25.	NA	Pristiq (desvenlafaxine)	Depression	4,039,000 (61%)

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Psychopharmacology as a way of life

- Modulation of mood by PP has become routine way for individuals to manage their lives
- Many non-psychiatric practices dependent on use of PP
  - Homes and wards for the elderly
  - Prisons
- This PP infused form of life is spreading to many regions

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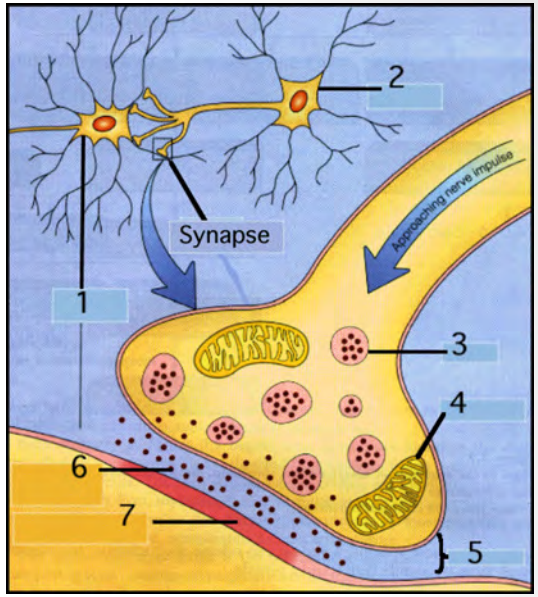
PAST DREAMS OF THE FUTURE

Mind not mystery but manipulable cerebral mechanism

A neuromolecular gaze

- A molecular vision of life in biomedicine
- Brain construed as an organ like any other
  - Anatomised into neurons, synapses, receptor sites, ion channels, etc. explained in terms of specific properties.
  -
- 'Normal' variations in perception, cognition and emotion envisaged at this level
  - blurs boundaries between states and traits, between psychology, psychiatry and neurology.
- Mental disorders and pathologies as anomalies within those molecular systems
  - blurs boundaries of organic vs. functional disorders.
- Manipulations of brain at this level
  - From molar (chemical cosh) to molecular (smart drug)
- Neuroreductionism as method and theory
  - "one cell at a time" in simple animals
  - But how to get from cell to system?



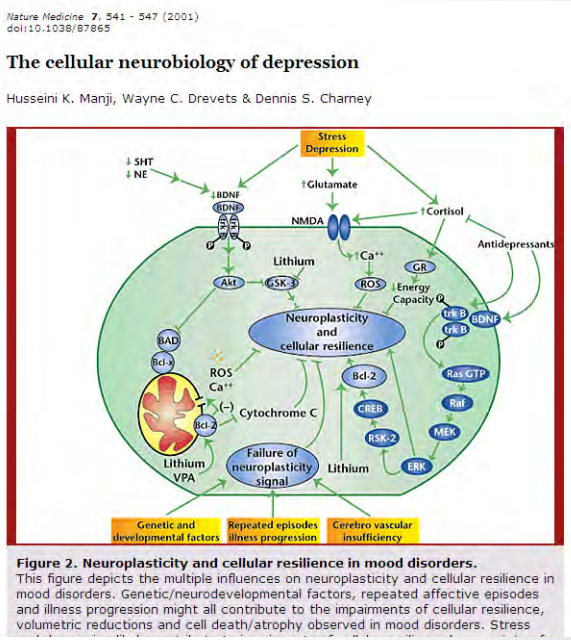


Figure 2. Neuroplasticity and cellular resilience in mood disorders. This figure depicts the multiple influences on neuroplasticity and cellular resilience in mood disorders. Genetic/neurodevelopmental factors, repeated affective episodes and illness progression might all contribute to the impairments of cellular resilience, volumetric reductions and cell death/atrophy observed in mood disorders. Stress

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The psychopharmacological imaginary

"Depression is not fully understood, but a growing amount of evidence supports the view that people with depression have an imbalance of the brain's neurotransmitters, the chemicals that allow nerve cells in the brain to communicate with each other. Many scientists believe that an imbalance in serotonin, one of these neurotransmitters, may be an important factor in the development and severity of depression. Prozac may help to correct this imbalance by increasing the brain's own supply of serotonin."

http://www.prozac.com/ HowProzacCanHelp/ HowItWorks.jsp

Normal

Depressed

On Prozac

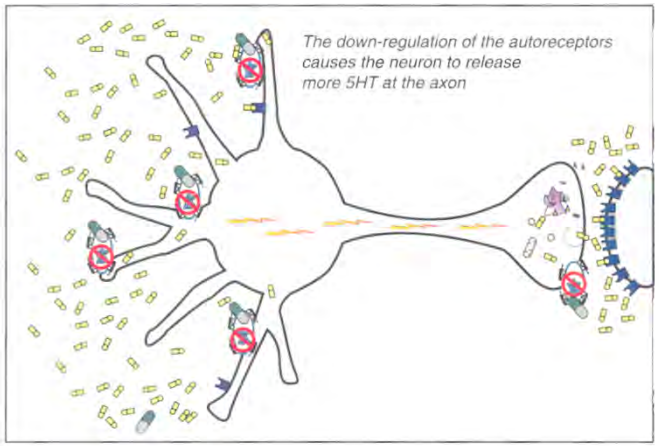

FIGURE 6–24. *Mechanism of action of serotonin selective reuptake inhibitors (SSRIs)* – part 4. Once the somatodendritic autoreceptors down-regulate as depicted in Figure 6–23, there is no longer

FIGURE 6–19. Shown here is the icon of a selective serotonin reuptake inhibitor (SSRI). In this case, four out of the five pharmacological properties of the TCAs (tricyclic antidepressants; Fig. 6–15) were removed. Only the serotonin reuptake inhibitor (SRI) portion remains; thus the SRI action is selective, which is why these agents are called selective SRIs.

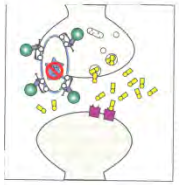

FIGURE 6–20. In this diagram, the SRI (serotonin reuptake inhibitor) portion of the SSRI molecule is shown inserted in the serotonin reuptake pump, blocking it and causing an antidepressant effect. This is analogous to one of the dimensions of the tricyclic antidepressants (TCAs), already shown in Figure 6–14.

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BUT …..

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Science 30 July 2010:
Vol. 329 no. 5991 pp. 502-504

In announcing the move to investors and analysts on 4 February, GSK Chief Executive Andrew Witty explained that pain, depression, and anxiety were areas where "we believe the probability of success is relatively low, [and] we think the cost of attaining success is disproportionately high." Ceasing research in these areas would save GSK £250 million ($387 million) by 2012. A few weeks later, news came that AstraZeneca was closing research facilities in the United States and Europe and ceasing drug-discovery work in schizophrenia, bipolar disorder, depression, and anxiety.

Is Pharma Running Out of Brainy Ideas?

Recent cutbacks raise concerns about the future of drug development for nervous system disorders

"The biggest problem isn't the announcements by GSK and AstraZeneca, it's when you look at the pipeline and see what companies are actually doing in psychiatric drug development," says Thomas Insel, director of the National Institute of Mental Health. "There are very few new molecular entities, very few novel ideas, and almost nothing that gives any hope for a transformation in the treatment of mental illness."

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HEALTH

R&D Cuts Curb Brain-Drug Pipeline

Development of new medicines for brain disorders could be threatened as major drug makers scale back research

GlaxoSmithKline, the U.K.'s biggest drug maker by sales and market capitalization, has reduced its discovery research in psychiatry and pain to focus on neurodegenerative and neuroinflammatory diseases such as dementia, multiple sclerosis and Parkinson's.

Explaining Glaxo's decision, Patrick Vallance, its chief of medicine R&D, told The Wall Street Journal that neuroscience research "is currently one of those of highest risk for the industry—the identification of targets, the animal models, the nature of experimental medicine and the development programs for these disease areas are amongst the least predictive and most costly of any area."

"Neurosciences research in many areas is very exciting but in some areas is not mature enough to make drug discovery efficient or effective today—which is why I believe that further investment is needed, and have argued the case for public-sector funding in this area," he says.

"Neuroscience has largely been a burial ground for drug development," says Nigel Gaymond, chief executive of the U.K.'s BioIndustry Association, a lobby group for British biotechnology companies

"Investors are demanding that drug companies now justify the billions of dollars they spend on research and development," according to Hakan Bjorklund, chief executive of privately held Nycomed of Switzerland. "It all has to do with R&D productivity," he told The Wall Street Journal.

Pharmaceutical Innovation in the 21st Century: New Drug approvals in the first Decade, 2000–2009

KI Kaitin and JA DiMasi

CliniCal pharmaCology & TherapeuTiCs | VOLUME 89 NUMBER 2 | fEBRUaRy 2011

"Neuropsychiatric disorders—including schizophrenia, depression, and Alzheimer's disease… are areas of enormous medical need….. Yet, despite the clear and compelling need for newer and better medications to treat these diseases, there is a paucity of innovation in this area. From a developmental standpoint, psychiatric diseases typically represent complex syndromes with multiple etiologies, and it is often difficult to measure end points. Preclinical screens are poor, and because the products are often used chronically, clinical studies are large and protocols are costly and complex"

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The failure of the dream

COMMENTARY

PSYCHIATRIC DRUG DISCOVERY

Revolution Stalled

Steven E. Hyman

Drug discovery is at a near standstill for treating psychiatric disorders such as schizophrenia, bipolar disorder, depression, and common forms of autism. Despite high prevalence and unmet medical need, major pharmaceutical companies are deemphasizing or exiting psychiatry, thus removing significant capacity from efforts to discover new medicines. In this Commentary, I develop a view of what has gone wrong scientifically and ask what can be done to address this parlous situation.

www.**ScienceTranslationalMedicine**.org 10 October 2012 Vol 4 Issue 155 155cm11

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Hyman: Revolution Stalled (Pt 1)

- In the period from 1993 to 2004, only 8% of central nervous system (CNS) drug candidates that reached the stage of initial human testing (phase 1) eventually achieved regulatory approval….
- Failures occurred occasionally because a significant toxicity emerged in late-stage clinical trials but more commonly because of an inability to demonstrate efficacy….
- European regulators have begun to demand either improvement in efficacy over existing drugs or biomarkers that identify patient subgroups for whom a new drug would be advantageous….
- many pharmaceutical companies have decided that the science to achieve these goals is lacking and that, for the time being, resources could be more productively spent on other disease areas. …
- Neither vast unmet medical need, nor large and growing markets, nor concerted sales campaigns that attempt to recast "me-too drugs" as innovative can illuminate a path across very difficult scientific terrain.

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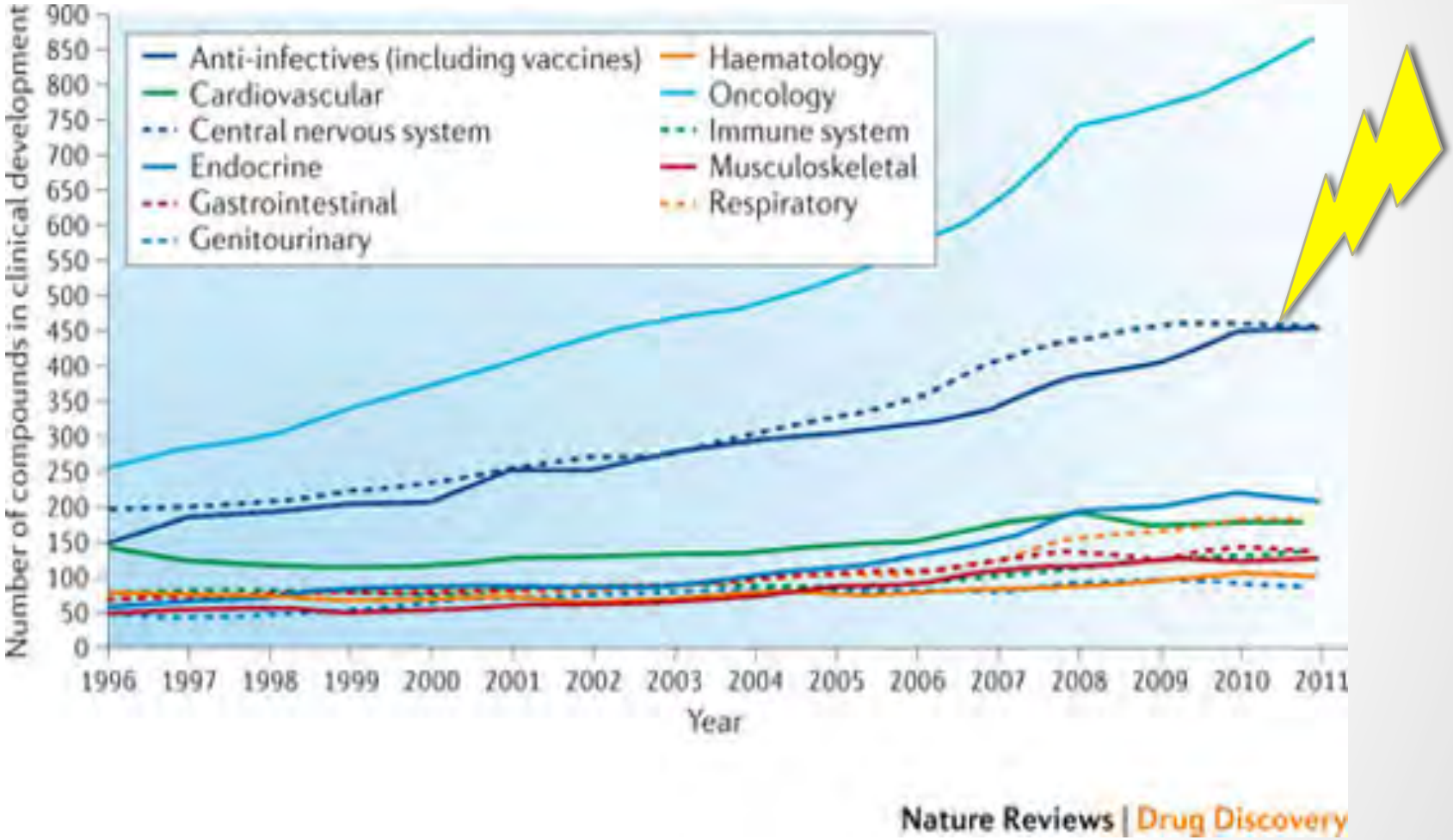
Figure 1 | **Compounds in clinical development by therapeutic area.**

The figure includes all innovative compounds between Phase I and Phase III development

The smallest therapeutic areas (dermatology, sensory, diagnostics and imaging, and other) were excluded for clarity. Source: Pharmaprojects Pipeline, 2011, Citeline, an Informa business;
see Supplementary information S1 (box) for details of data sources and analysis.

Nature Reviews Drug Discovery, VOLUME 11 | JUNE 2012 , 435-6.



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Hyman: Revolution Stalled (Pt. 2)

- Compared with other areas of translational medicine, psychiatry finds itself with few, if any, validated molecular targets. …
- Current animal-based assays have failed to identify efficacious drugs with new molecular mechanisms, and given scant understanding of the pathophysiology of common psychiatric disorders, it is difficult to develop better models….
- Without [objective diagnostic tests], clinical trials of psychiatric treatments are dependent on disease definitions grounded in the descriptive psychiatry of the 1960s and 1970s (23) as well as on subjective rating scales …
- The best-recognized obstacles to effective clinical translation in psychiatry include the complexity of the brain and the associated challenge of connecting levels of analysis from molecules to cells, synapses, circuits, and thence to higher cognition, emotion regulation, and executive function.

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- CNS Disorders. Only 5 years ago, the number of CNS drugs in the pipeline was almost identical to that of cancer drugs (between 270 and 280).
- In 2013, that number is 50% lower, although CNS drugs are still second to cancer drugs in terms of sheer numbers in the pipeline.
  - The 5 CNS drugs that are scheduled for approval by the FDA in 2013 … include Levadex (dihydroergotamine), an oral inhaler for acute migraine (delayed from last year); levomilnacipran, a serotonin norepinephrine reuptake inhibitor (SNRI) for the treatment of depression, that has shown greater potency and selectivity for norepinephrine than other SNRIs; suvorexant, with a new mechanism of action for primary insomnia; Brintellix (vortioxetine), which has shown mixed efficacy data for major depressive disorders; and cariprazine, an atypical antipsychotic for schizophrenia, with a mechanism similar to Abilify but potentially with an improved safety profile.

Trends in the 2013 Pharmaceutical Pipeline
April 2013 Vol 6 No 3 Payers' Guide to New FDA Approvals (/issues/2013/april-2013-vol-6-no-3-payers-guide-to-new-fda-approvals)

The pipeline is not healthy

- The pipeline seems healthy for many psychiatric conditions
- BUT many of these are approved drugs being trialled for new conditions
- Many are 'atypical' psychotics whose mode of action is disputed
- Others have similar problems – drugs approved for other conditions that have effects on neurotransmitters
- Many existing drugs going out of patent
- Costs of R&D are rising, and CNS drugs take longer to bring to market than other drugs
- CNS drugs tend to fail in late stage clinical trials
- Animal models are misleading
- Therefore companies are investing in other areas such as oncology and autoimmune disease.

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But don't despair…

- Better diagnosis by hypothesis free data collection and analysis
- Advances in genetics
  - Whole genome sequencing, optogenetics, epigenetics
- Research with neuronal circuits cultivated in vitro (hESC, iPSC)
- …….

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TODAY'S DREAMS OF THE FUTURE

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"THE PROBLEM IS DIAGNOSIS"….

Towards personalised psychiatry

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Psychiatric Dreams of the 2000s: Steven Hyman, 2003

- "By combining neuroimaging with genetic studies, physicians may eventually be able to move psychiatric diagnoses out of the realm of symptom checklists and into the domain of objective medical tests.
- Genetic testing of patients could reveal who is at high risk for developing a disorder such as schizophrenia or depression.
- Doctors could then use neuroimaging on the high-risk patients to determine whether the disorder has actually set in.
- I do not want to sound too optimistic--the task is daunting. But the current pace of technological development augurs well for progress."

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The dream is over…? Steven Hyman (2008)

- "Common diseases … represent families of diseases that share major pathophysiological and symptomatic features, but can differ in important ways
- Similar neuropsychiatric symptoms can result from different combinations of genetic risk factors [and] that the same genetic variant may be associated with multiple DSM-IV diagnoses….
- Identification of common risk-conferring variants has … proved extremely challenging … because of their relatively small contribution to the disease phenotype [and] the diverse genetic, environmental … factors that lead to these common disease"
- No clear boundaries between ill and well….
- No simple 'genomic' disorders in psychiatry ….

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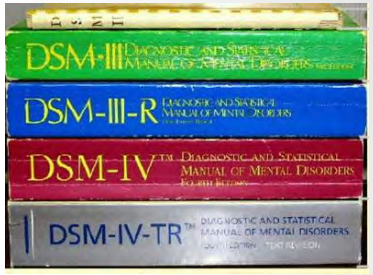
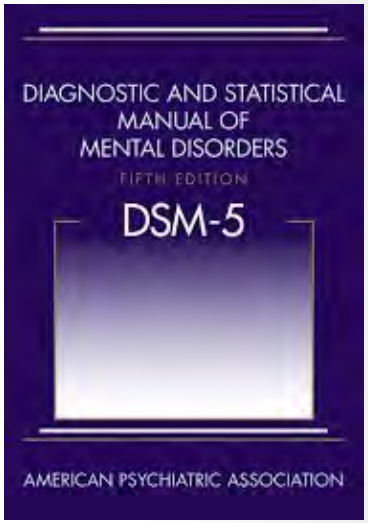
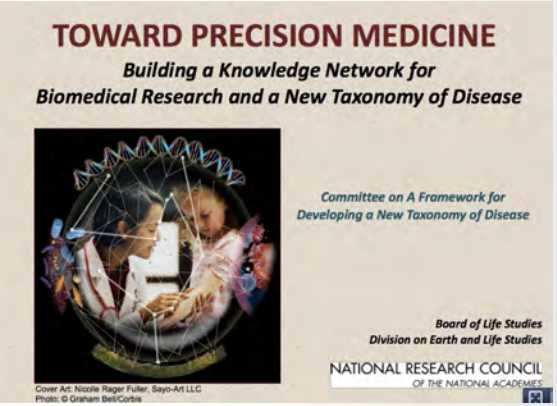
Personalisation in psychopharmacology?



- DSM 5 – May 2013:
  - not a single clinically useful validated genomic biomarker for any psychiatric disease
- Clinicians sceptical
  - doubt about role of genomic screening for susceptibility (or for clinical use)
- Personalisation postponed
  - From personalisation to 'stratification' or 'precision'
- But the the dream lives on….





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Back to the future?

- June 2011: NIMH sets out its Research Domain Criteria
  - Acknowledged failure to ground DSM categories in brain
  - Buy "could specificity in fact exist, but not for the currently recognized clinical categories?".
- April 2013: Thomas Insel announced
  - "NIMH will be re--orienting its research away from DSM categories" on the grounds that "Mental disorders are biological disorders involving brain circuits that implicate specific domains of cognition, emotion or behavior'
- It is in terms of these that diagnosis should proceed and towards these that treatment should be targeted.
  - "But patients and families should welcome this change as a first step towards "**precision medicine**," the movement that has transformed cancer diagnosis and treatment."
- Trust in the brain, not in DSM .

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Brain signatures in the HBP

The Medical Informatics Platform of the HBP aims to

- build the tools to federate clinical data, including genetics and imaging, currently locked in hospital and research archives
- develop tools making it possible to extract unique biological signatures of disease from multi-level data for patients with many different disorders
- develop a new, comprehensive classification of brain diseases, based on parameterised combinations of biological features and markers.
- a new category of biologically based diagnostics, supported by strong mechanistic hypotheses of disease causation.
- Disease signatures for reconstructing models of disease and performing in silico experiments to develop new targets and new strategies for treatment.
- Brain simulation to predict the desirable and adverse effects of treatments, before expensive programmes of animal experimentation or human trials.

Human Brain Project

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THE LURE OF ALZHEIMER'S

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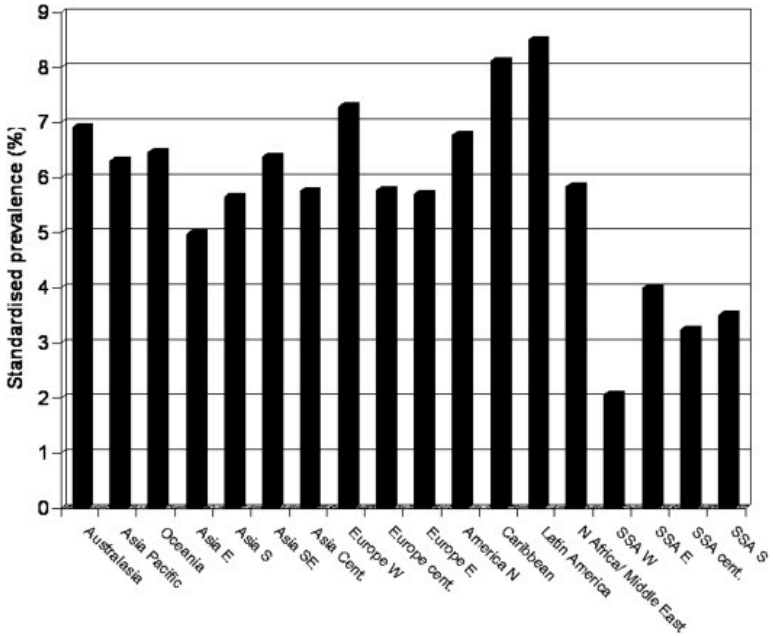
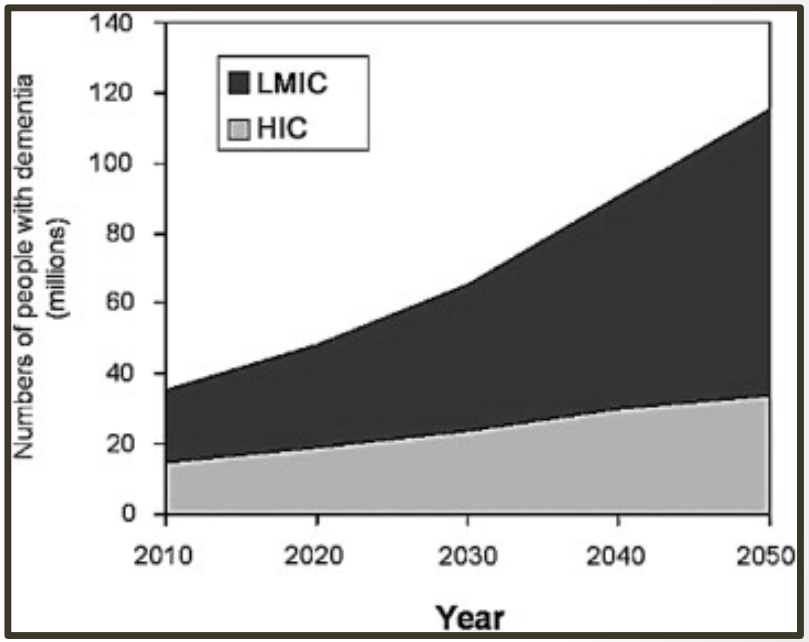
The global prevalence of dementia

Alzheimer's & Dementia:
The Journal of the Alzheimer's Association
Volume 9, Issue 1 , Pages 63-75.e2, January 2013



Estimated prevalence of dementia for those aged ≥60 years, standardized to the Western Europe population, by Global Burden of Disease region.



The growth in numbers of people with dementia in high-income (HIC) and low- and middle-income countries (LMIC).

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FROM THE ANALYST'S COUCH

Alzheimer's disease market: hope deferred

Zelicia Gerald and Waldemar Ockert

Current developmental pipeline

Currently, discounting university and public research programmes, 102 drugs are in clinical trials for the treatment of AD. These mainly consist of neuromodulatory signalling or A β -targeting therapies

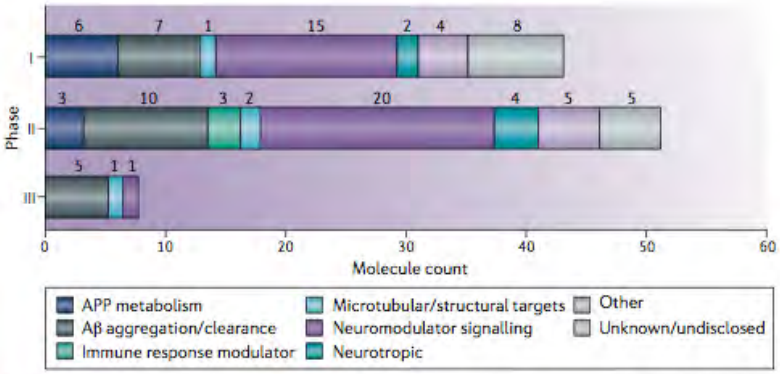

Figure 1 | **The mode of action categories of developmental drugs across clinical Phase I, II and III trials.** Source: GBI Research proprietary database.

However trials have largely been disappointing and often discontinued

Market outlook

Over the next 6 years, a decline in the AD market from US$4.2 billion in 2012 to approximately $3.8 billion in 2018 is expected even if Gammagard is approved, as many of the currently marketed products already have or are set to reach their patent expiries across the seven major developed markets (the United States, United Kingdom, Germany, France, Italy, Spain and Japan) in the near future (FIG. 2). However, despite the disappointing track record of A β -targeting agents in the recent past, there is a small silver lining on the horizon. The potential for earlier diagnosis and earlier clinical intervention to slow or prevent neurotoxicity, inflammation and synaptic dysfunction may actually be the beginning of meaningful hope for AD sufferers. However, it is likely to take another half of a decade before this might begin to become a reality.

Nature Reviews Drug Discovery: Volume 12, January 2013, p. 19

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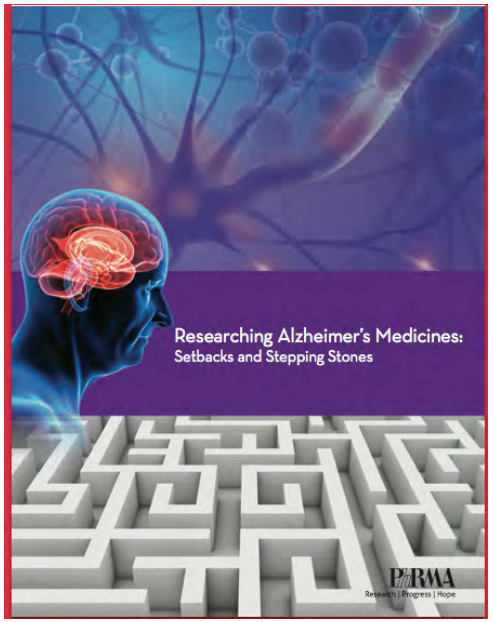

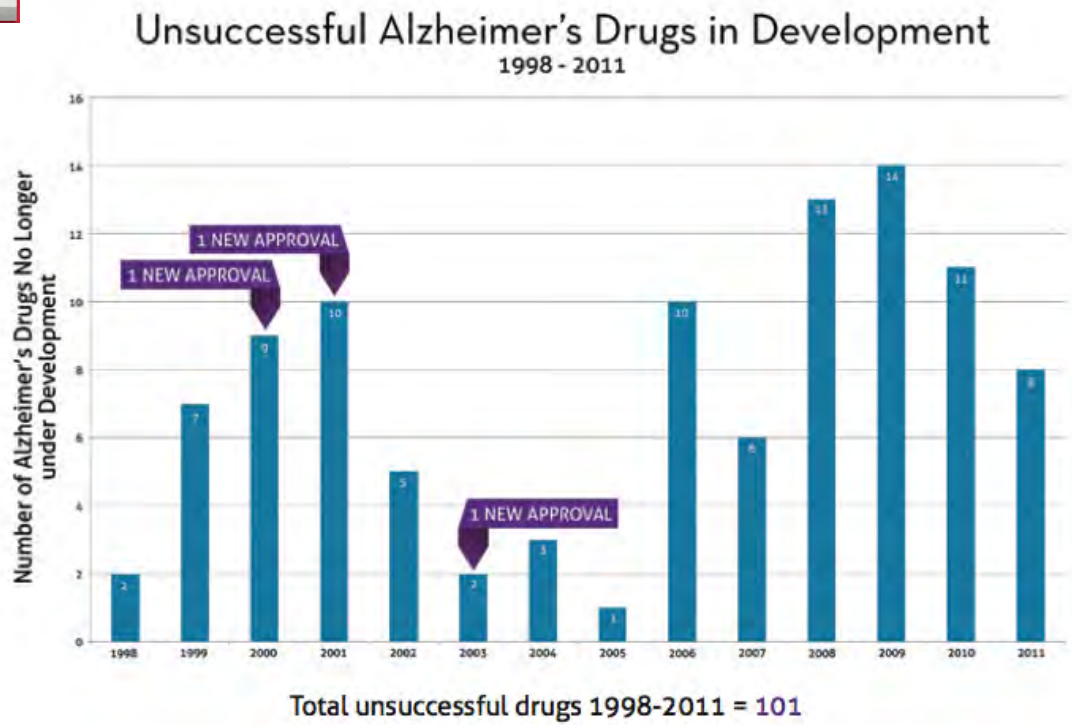

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Action Points

- Detailed results from an aborted phase III trial of semagacestat, a drug aimed at slowing Alzheimer's disease, were published but the major finding remained as previously announced -- it didn't work.
- Note that semagacestat was one of numerous drugs targeting beta-amyloid protein, which forms insoluble plaques in the brains of Alzheimer's disease patients.

The New York Times

Business Day

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Alzheimer's Treatment Failed Trial, Maker Says

By ANDREW POLLACK
Published: May 7, 2013

In yet another setback for the treatment of Alzheimer's disease, Baxter International said Tuesday that its drug, Gammagard, had failed to halt the mental decline caused by the disease in a late-stage clinical trial.

Prospects that the drug might have some effect brightened last year when researchers reported that four patients who had received the maximum dose had gone three years without any decline in several measures of cognition and daily functioning, which they termed highly unusual.

But as is often the case, anecdotal evidence failed to hold up when the treatment was subject to a large, randomized trial against a placebo.

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Alzheimer's Drug Fails a Late-Stage Clinical Trial

The disappointing results of a highly anticipated Alzheimer's drug by Pfizer is a setback for the field, but not necessarily surprising

By Alexandra Sifferlin @acsifferlin | July 24, 2012 | 3 Comments

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Ursula Markus / Getty Images

A highly anticipated trial of an experimental Alzheimer's drug failed its first large clinical trial, Pfizer, one of the companies developing the new treatment, announced on Monday.

The disappointing findings once again call into question the leading theory about what causes the memory-robbing disease: accumulation of a naturally occurring protein called beta amyloid is thought to gum up the brain and cause the nerve death and cognitive decline associated with Alzheimer's. Indeed, a study published earlier this month found that a rare gene mutation that reduces beta amyloid production appears to protect people from developing the disease. But numerous experimental drugs — including the latest, known as bapineuzumab — that target beta amyloid have failed in trials to improve memory or cognitive functioning in Alzheimer's patients.

According to Pfizer, which is developing bapineuzumab with Johnson & Johnson and Irish pharmaceutical company Elan, the new drug also did not improve cognition or daily function compared with a placebo in participants of a phase 3 trial. The drug was tested on 1,100 Americans with mild to moderate disease.

RELATED

Alzheimer's Drug Fails Its First Big Clinical Trial *The New York Times*

Pfizer, J&J Alzheimer's Drug Fails One of Four Big Trials *Reuters*

Setback for Alzheimer's Drug *The Wall Street Journal*

Topics: Clinical Trials | Pipeline

UPDATED: Eli Lilly racks up another Alzheimer's failure after BACE drug sparks safety fears

June 13, 2013 | By John Carroll

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STRAIGHT TO THE BRAIN?

From chemistry to electricity and magnetism

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From drugs to devices?

- Deep brain stimulation (DBS)
- Transcranial magnetic stimulation (TMS)
- Transcranial direct current stimulation (TDCS)
- Transcranial alternating current stimulation (TACS)
- Neural stem cells

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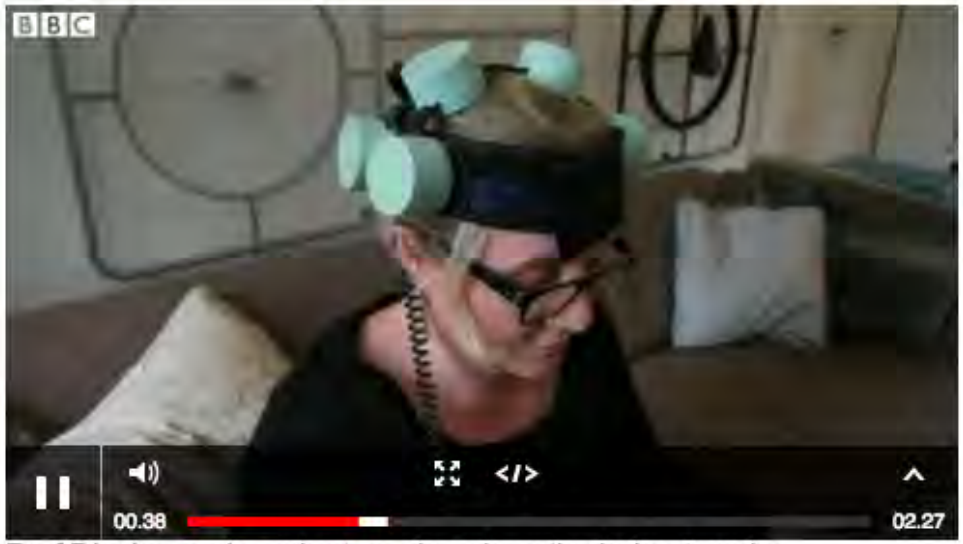
Depression treatment technique uses new helmet therapy

By Malcolm Brabant
BBC News



Prof Dissing and a volunteer show how the helmet works

A helmet that delivers electro-magnetic impulses to the brain has shown promise in treating people with depression, Danish researchers have said.

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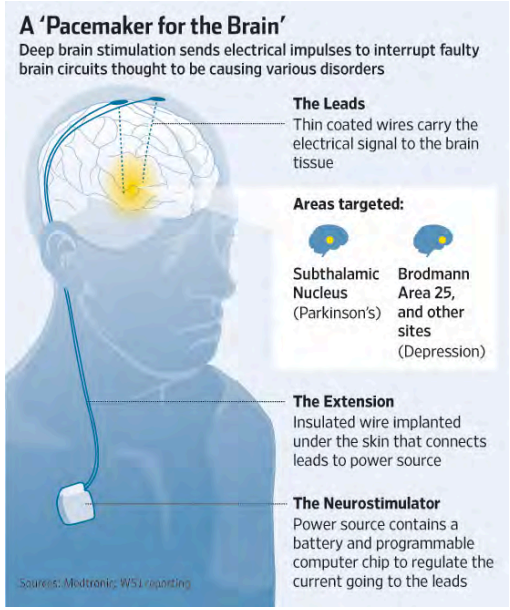
A 'Pacemaker for the Brain'
Deep brain stimulation sends electrical impulses to interrupt faulty brain circuits thought to be causing various disorders
The Leads
Thin coated wires carry the electrical signal to the brain tissue
Areas targeted:
Subthalamic Nucleus (Parkinson's)
Brodmann Area 25, and other sites (Depression)
The Extension
Insulated wire implanted under the skin that connects leads to power source
The Neurostimulator
Power source contains a battery and programmable computer chip to regulate the current going to the leads
Sources: Medtronic; WSJ reporting

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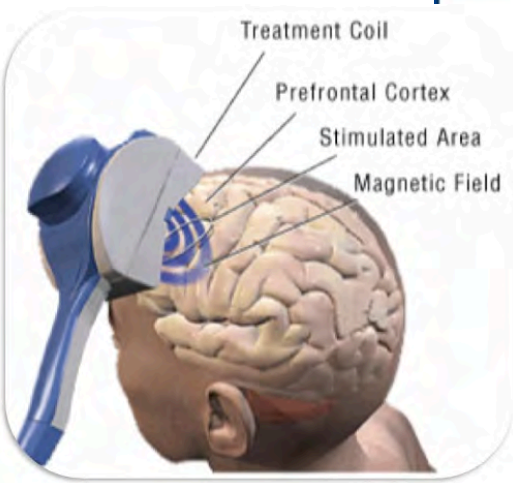
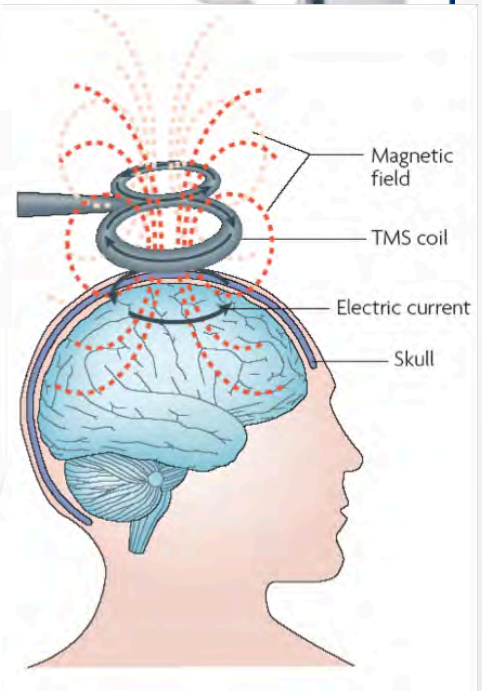

Treatment Coil
Prefrontal Cortex
Stimulated Area
Magnetic Field


Magnetic field
TMS coil
Electric current
Skull

BUT….

- Modes of action largely unknown
- Large scale trials not conducted
- Regulation of medical devices problematic
- Will devices not drugs, be the next best hope?
- And will the story repeat itself?

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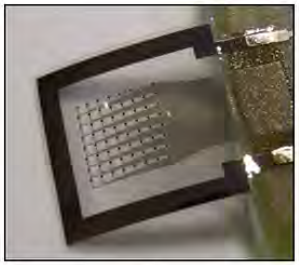
MIT Technology Review

Military Funds Brain-Computer Interfaces to Control Feelings

A $70 million program will try to develop brain implants able to regulate emotions in the mentally ill.

By Antonio Regalado on May 29, 2014



Brain reader: An array of micro-electrodes printed on plastic can record from the brain's surface. It is 6.5 millimeters on a side.

Researcher Jose Carmena has worked for years training macaque monkeys to move computer cursors and robotic limbs with their minds. He does so by implanting electrodes into their brains to monitor neural activity. Now, as part of a sweeping $70 million program funded by the U.S. military, Carmena has a new goal: to use brain implants to read, and then control, the emotions of mentally ill people.

This week the Defense Advanced Research Projects Agency, or DARPA, awarded two large contracts to Massachusetts General Hospital and the University of California, San Francisco, to create electrical brain implants capable of treating seven psychiatric conditions, including addiction, depression, and borderline personality disorder.

CORTERA NEUROTECHNOLOGIES

Under the contracts, which are the largest awards so far supporting President Obama's BRAIN Initiative, the brain-mapping program launched by the White House last year, UCSF will receive as much as $26 million and Mass General up to $30 million. Companies including the medical device giant Medtronic and startup Cortera Neurotechnologies, a spin-out from UC Berkeley's wireless laboratory, will supply technology for the effort. Initial research will be in animals, but DARPA hopes to reach human tests within two or three years.

The research builds on a small but quickly growing market for devices that work by stimulating nerves, both inside the brain and outside it. More than 110,000 Parkinson's patients have received deep-brain stimulators built by Medtronic that control body tremors by sending electric pulses into the brain. More recently, doctors have used such stimulators to treat severe cases of obsessive-compulsive disorder (see "Brain Implants Can Reset Misfiring Circuits"). Last November, the U.S. Food & Drug Administration approved NeuroPace, the first implant that both records from the brain and stimulates it (see "Zapping Seizures Away"). It is used to watch for epileptic seizures and then stop them with electrical pulses. Altogether, U.S. doctors bill for about $2.6 billion worth of neural stimulation devices a year, according to industry estimates.

Researchers say they are making rapid improvements in electronics, including small, implantable computers. Under its program, Mass General will work with Draper Laboratories in Cambridge, Massachusetts, to develop new types of stimulators. The UCSF team is being supported by microelectronics and wireless researchers at UC Berkeley, who have created several prototypes of miniaturized brain implants. Michel Maharbiz, a professor in Berkeley's electrical engineering department, says the Obama brain initiative, and now the DARPA money, has created a "feeding frenzy" around new technology. "It's a great time to do tech for the brain," he says.

DOES PSYCHOPHARMACOLOGY HAVE A FUTURE?

And if so, what will that be?

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Thank you for your attention !

- With thanks to:
  - Cameron Spence
  - Stuart Hogarth

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