Challenges and Opportunities for Integration of Therapeutic Devices into Psychiatry

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Opinions are my own
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Principles

- Therapeutics provide value to patients, caregivers, & society
- Compensation for value should not depend on type of therapeutic, rather the extent of the value provided

- Corollary: equivalent data should lead to equivalent adoption, utilization, reimbursement and commensurate success of technology
  - Otherwise barriers must exist and must be overcome for the good of patients

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Table 2. Effect sizes and levels of significance for all individual drug-placebo comparisons

Trial	Treatment	Baseline mean (s.d.)		Endpoint mean (s.d.)		Effect size		P-value		
		HDRS-17	DM	HDRS-17	DM	HDRS-17	DM	HDRS-17[a]	DM[a]	DM[b]
GSK/002	PRX IR FLEX	23.9 (4.2)	2.6 (0.6)	13.9 (8.5)	1.4 (1.1)	0.46	0.56	**<0.001**	**<0.001**	**<0.001**
	PLA	23.6 (3.6)	2.7 (0.6)	17.3 (8.2)	1.9 (1.1)					
GSK/003	PRX IR FLEX	23.5 (3.7)	2.9 (0.5)	14.6 (7.5)	1.8 (1.0)	0.53	0.60	**<0.001**	**<0.001**	**<0.001**
	PLA	23.5 (3.5)	2.9 (0.5)	18.4 (7.7)	2.3 (1.0)					
GSK/115	FLX FLEX	22.5 (3.6)	2.7 (0.7)	14.8 (6.8)	1.6 (1.0)	0.08	0.31	0.50	**0.006**	**0.01**
	PRX IR FLEX	22.5 (3.7)	2.8 (0.7)	15.0 (7.1)	1.6 (1.1)	0.06	0.28	0.58	**0.01**	**0.01**
	PLA	21.8 (4.0)	2.7 (0.6)	14.7 (7.3)	1.9 (1.2)					
GSK/128	FLX FLEX	23.0 (3.7)	2.8 (0.7)	13.4 (7.0)	1.4 (1.1)	0.28	0.40	**0.007**	**<0.001**	**<0.001**
	PRX IR FLEX	23.1 (3.9)	2.9 (0.6)	13.8 (7.1)	1.5 (1.2)	0.22	0.31	**0.03**	**0.003**	**0.003**
	PLA	23.2 (3.7)	2.7 (0.7)	15.5 (7.6)	1.8 (1.2)					
GSK/251	PRX IR FLEX	22.2 (3.5)	2.8 (0.6)	13.7 (6.7)	1.5 (1.1)	0.14	0.32	0.29	**0.01**	**0.01**
	PLA	22.1 (3.3)	2.9 (0.5)	14.5 (7.4)	1.8 (1.1)					
GSK/448	PRX CR FLEX	23.0 (2.6)	2.8 (0.6)	12.5 (6.4)	1.3 (1.0)	0.23	0.52	0.12	**<0.001**	**<0.001**
	PRX IR FLEX	23.4 (2.8)	2.9 (0.6)	14.1 (7.2)	1.6 (1.2)	0.02	0.34	0.90	**0.02**	**0.01**
	PLA	23.4 (2.9)	2.9 (0.6)	14.1 (6.7)	1.9 (1.0)					
GSK/449	PRX CR FLEX	23.8 (3.4)	2.9 (0.6)	12.6 (7.2)	1.4 (1.0)	0.35	0.43	**0.01**	**0.002**	**0.001**
	PRX IR FLEX	23.7 (3.1)	2.9 (0.6)	13.2 (7.2)	1.3 (1.1)	0.25	0.51	0.07	**<0.001**	**<0.001**
	PLA	23.5 (3.1)	2.8 (0.6)	14.8 (6.8)	1.8 (1.1)					
GSK/487	PRX CR FLEX	22.1 (3.5)	2.7 (0.6)	12.2 (6.7)	1.4 (1.0)	0.25	0.34	0.07	**0.01**	**0.01**
	PRX IR FLEX	22.3 (3.1)	2.8 (0.6)	12.1 (6.4)	1.4 (1.0)	0.28	0.30	**0.04**	**0.03**	**0.02**
	PLA	22.1 (3)	2.7 (0.6)	13.6 (6.4)	1.7 (1.1)					
GSK/810	PRX CR 12.5	23.2 (2.9)	2.8 (0.5)	11.7 (6.8)	1.4 (1.0)	0.34	0.29	**0.004**	**0.02**	**0.008**
	PRX CR 25	23.5 (3.3)	2.7 (0.5)	11.1 (7.1)	1.2 (1.0)	0.45	0.50	**<0.001**	**<0.001**	**<0.001**
	PLA	23.8 (3.2)	2.8 (0.5)	14.4 (7.6)	1.7 (1.0)					
GSK/874	PRX CR 12.5	22.6 (3.6)	2.8 (0.5)	13.6 (7.0)	1.6 (1.1)	0.20	0.33	0.07	**0.003**	**0.002**
	PRX CR 25	23.1 (3.9)	2.8 (0.6)	14.1 (6.5)	1.5 (1.0)	0.35	0.46	**0.001**	**<0.001**	**<0.001**
	PLA	22.7 (4)	2.8 (0.6)	17.1 (7.4)	1.8 (1.0)					
LB/85A	CIT FLEX	23.8 (3.2)	2.7 (0.7)	14.4 (7.9)	1.3 (1.0)	0.36	0.51	**0.02**	**0.001**	**0.001**
	PLA	24.0 (3.5)	2.7 (0.7)	14.8 (6.7)	1.8 (1.0)					
LB/89303	CIT 20	24.3 (6.7)	2.8 (0.7)	13.2 (10.6)	1.6 (1.1)	0.02	0.08	0.90	0.67	0.84
	CIT 40	23.0 (6.2)	2.7 (0.7)	9.7 (8.8)	1.1 (1.0)	0.36	0.56	**<0.05**	**0.003**	**0.003**
	PLA	23.7 (6.1)	2.8 (0.7)	13.2 (9.6)	1.7 (1.1)					
LB/91206	CIT 10	22.2 (3.5)	2.9 (0.5)	12.6 (8.1)	1.4 (1.2)	0.19	0.37	0.14	**0.004**	**0.003**
	CIT 20	21.7 (2.9)	2.9 (0.5)	13.0 (7.3)	1.5 (1.2)	0.05	0.30	0.67	**0.02**	**0.006**
	CIT 40	22.1 (3.3)	2.9 (0.5)	11.8 (8.0)	1.3 (1.2)	0.30	0.42	**0.02**	**<0.001**	**<0.001**
	CIT 60	21.8 (3.2)	2.9 (0.5)	11.8 (6.7)	1.2 (1.1)	0.25	0.52	>0.05	**<0.001**	**<0.001**
	PLA	21.9 (3.4)	2.8 (0.6)	13.6 (6.9)	1.8 (1.1)					
PZ/103	SER 50 mg	24.9 (3.0)	2.9 (0.7)	14.6 (8.8)	1.6 (1.2)	0.30	0.47	**<0.05**	**0.002**	**0.002**
	SER 100 mg	24.7 (2.9)	3.0 (0.7)	15.1 (9.0)	1.7 (1.3)	0.23	0.44	0.12	**0.004**	**0.002**
	SER 200 mg	25.8 (3.4)	3.0 (0.6)	15.9 (9.4)	1.7 (1.2)	0.24	0.46	0.13	**0.004**	**0.003**
	PLA	25.3 (2.9)	3.0 (0.6)	17.4 (8.4)	2.2 (1.2)					
PZ/104	SER FLEX	23.3 (3.7)	2.8 (0.5)	12.5 (8.2)	1.4 (1.1)	0.34	0.38	**0.004**	**0.002**	**0.001**
	PLA	23.4 (3.7)	2.8 (0.6)	15.2 (8.0)	1.8 (1.2)					
PZ/109	SER FLEX	22.0 (3.4)	2.6 (0.6)	13.3 (7.8)	1.4 (1.1)	0.10	0.13	0.48	0.37	0.38
	PLA	21.5 (3.4)	2.7 (0.5)	13.6 (8.0)	1.6 (1.2)					
PZ/111	FLX FLEX	24.4 (2.4)	2.9 (0.5)	13.4 (7.0)	1.4 (1.1)	0.08	0.45	0.56	**0.001**	**<0.001**
	SER FLEX	24.1 (1.9)	2.9 (0.4)	12.8 (6.9)	1.5 (1.1)	0.14	0.43	0.31	**0.002**	**0.001**
	PLA	24.2 (2.2)	2.9 (0.3)	13.8 (7.5)	1.9 (1.0)					
PZ/315	SER FLEX	23.1 (4.2)	2.6 (0.7)	14.5 (8.8)	1.6 (1.0)	0.15	0.10	0.39	0.56	0.39
	PLA	22.2 (4.4)	2.6 (0.8)	15.4 (7.8)	1.8 (1.1)					

Abbreviations: CIT, citalopram; FLEX, flexible dosage; FLX, fluoxetine; PLA, placebo; PRX CR, paroxetine continuous release; PRX IR, paroxetine immediate release; SER, sertraline. For bold values $P < 0.05$. [a]P-value obtained from an ANCOVA-model. [b]P-value obtained from an ordinal logistic regression model.

Summary of studies of SSRI's in MDD

	SSRI Effect size
High	0.53
Low	0.02
median	0.24

An estimated 35% of patients are treatment resistant: many are refractory to 2 or more medicines

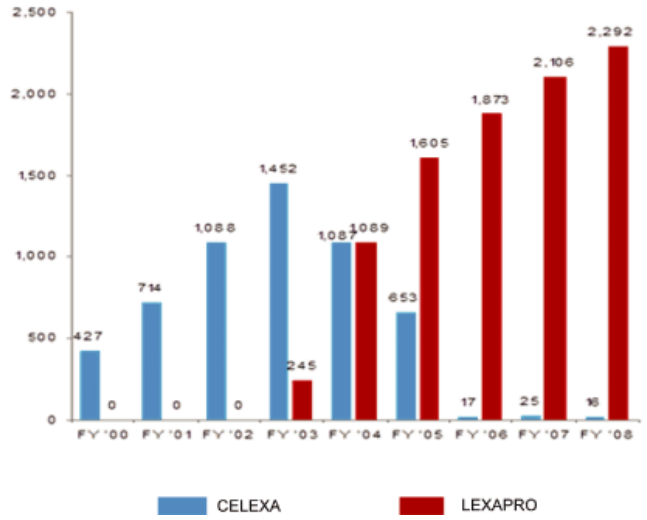
TMS Studies in Treatment resistant depression vs Drug Studies in Major depressive disorder

Platform footprint	Clinical performance			
	Tx protocol	Efficacy		Safety
		Response	Remission	
 • Portable cart that includes a dTMS helmet • Patient sits in a chair (not included) • Requires a separate treatment room	• 20 min Tx • 5x per week • 4 weeks	38.4% vs. 21.4% sham (p=0.0138) via HDRS-21	32.6% vs. 14.6% sham (p=0.0051) via HDRS-21	1 seizure** and higher incidence of application site pain (5%) vs. sham (0%)
 • Portable cart • Adjustable TMS stimulator arm • Patient lays on chair (included) • Requires a separate treatment room	• 37.5 min Tx • 5x per week • 6 weeks	23.9% vs. 12.3% sham (p=0.0096) via MADRS	14.2% vs. 5.5% sham (p=0.0117) via MADRS	Higher incidence of application site pain (35.8%) vs. sham (3.8%)
 • Stationary device • Adjustable TMS stimulator arms • Patient lays on treatment table • Requires a separate treatment room	• 37.5 min Tx • 5x per week • 4 weeks	55.3% vs. 32.4% sham (p=0.063) via HAMD-24	26.3% vs. 18.9% sham (p=0.58) via HAMD-24	Higher incidence of pain at treatment site (10%) vs. sham (0%)
 • Stationary sTMS* device that slides into position • Patient lays on treatment table • Requires a separate treatment room	• 30 min Tx • 5x per week • 6 weeks	39.0% vs. 21.3% sham (p=0.036) via MADRS	18.6% vs. 14.8% sham (n.s.) via MADRS	No significant differences vs. sham

	SSRI Effect size	TMS Effect size
High	0.53	0.76
Low	0.02	0.29
median	0.24	0.42

Studies in patients who have failed at least 1 and up to 4 antidepressants

Market success comparison



Total CELEXA & LEXAPRO Sales
Fiscal Year End (March 31)
$MM

Forest Labs, 2011 proxy statement, SEC website link

Uptake and utilization of TMS has been much slower

Why the marked difference in market success given the superior data in treatment resistant patients?

Methods

- Examination of non-invasive neurostimulation devices and business opportunities
- Workshops & interviews with sponsors, medical/ scientific experts, payors, VC investors
- Market research with physicians, users and non-users
- Development of a forecast model and strategic plan

Patterns of practice and preferences among Psychiatrists

- Many are willing to refer for advanced care with caveats because referral practices are currently limited
- Few are willing to open a procedure-based practice with need for extra space, hiring of technicians, medical oversight—insufficient space for potential referral demand
- Economic challenges: cost of device vs lease model, insufficient patients in practice to break even
- Need to get referrals, reluctance to advertise, concern about competition with other centers
- Many not convinced that medicines and psychotherapy would not be eventually effective much of the time

Patient factors

- Many outpatients are reluctant to show up daily for up to 20 sessions with 2/week maintenance
  - Minimal drive time acceptable (<30 min)
  - Concern over duration of appointment
  - Slowness of response to therapy is a concern and cause for discontinuation
- Patient segmentation
  - TMS not available until multiple drugs tried
  - Exclusions for some conditions
- Few can afford TMS and most rely on insurance coverage
  - Sensitivity to co-pay

Reimbursement issues

- Reimbursement growing in the US: estimated >210 MM covered lives.
  - Not all regions of Medicare/Medicaid
  - Little coverage ex-US
- In many cases, documenting treatment failure is required and can be onerous for MD's
  - Low tier of coverage, prior approval, high co-pay
- Reimbursement experts cited limited dataset
  - Small efficacy studies,
  - lack of H2H with SOC
  - uncertainty about place in the treatment algorithm
  - Little long term data elucidating extent of use (e.g., yearly)

Device based therapy is expensive

Coding and Payment: Medicare National Average Physician Fee Schedule 2012/2013:

CPT code	2012 MD payment (in-office)	2012 MD payment (in hospital	2013 MD payment
90867	$ 346.84	$ 173.59	Therapeutic repetitive transcranial magnetic stimulation (rTMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
90868	$ 169.85	$ 23.83	Subsequent delivery and management, per session
90869	$ 422.75	$ 115.73	Subsequent MT re-determination with delivery and management

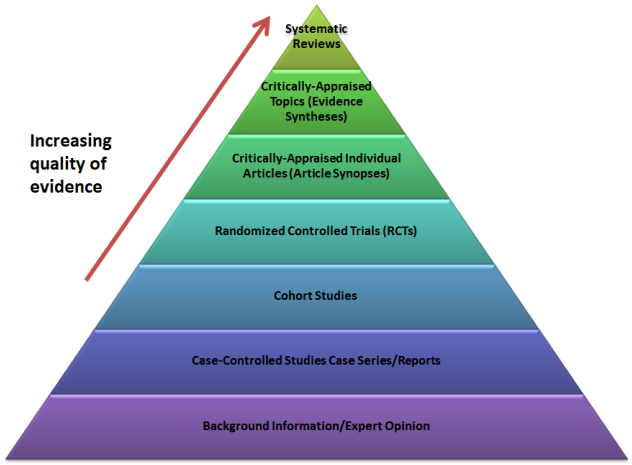
Most antidepressants are generic and inexpensive*

> Retail prices for commonly prescribed antidepressants range from about $21 a month, and sometimes even less, to more than $1,000 a month. This report shows how you can save more than $100 a month or $1,200 a year, if you have to take an antidepressant regularly.

Consumer reports Best Buy Drugs, 2013

$4000 for lowest priced TMS vs <$1000 retail for an antidepressant
Devices cost $100,000 to 200,000 and may be purchased or leased

Developing convincing evidence for payors, physicians and patients



American Psychiatric Association (2010)

"...Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or light therapy..."

- ***"High strength of evidence" for efficacy from well-controlled RCTs***

Agency for Healthcare Research and Quality: Comparative Effectiveness Report on Non-Pharmacologic Treatments for Depression , October 2011

Evidence generation is slow compared to medicines: smaller investment and more rapid approval cycle

Drugs:
$ 873M without failures
13.5 years

Devices:
Estimated costs: $3-20 MM
Duration: 3-5 years class 2
5-10 years class 3

Solutions and implications for multimodal therapies

- For expensive therapies: build evidence for payers and professional societies, not just for FDA
  - Need a richer dataset to convince all parties
  - H2H data with alternatives or Standard of Care
  - Provide evidence of durability of efficacy
- Evolve practice patterns in psychiatry to utilize more types of medical interventions, or
- Enhance use of alternative models to jump start uptake
  - Alternative providers of care: treatment centers, neurologists or other doctors
- Develop 21st century alternatives that are more mobile, less expensive, or require less medical supervision

Thank you

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Key messages

- Despite apparently solid efficacy data, devices for depression have not enjoyed widespread use
- Factors limiting uptake
  - Psychiatry practice patterns, Patient convenience and preference, reimbursement patterns, competitive factors, & level of evidence
- Solutions and implications for multimodal therapies:
  - Better evidence generation
  - Evolve practice patterns in psychiatry
  - Develop improved devices for the 21st century