



Medicines Chest

December 2013

David Nutt

Gavin Kilpatrick



Background

- Many pharmaceutical companies have disinvested in the neuroscience field due to the perceived high risk of failure.
- As a result, the development of many novel compounds has been halted and the compounds shelved.
- Such compounds may not necessarily be useful drugs, but many have important and selective actions that mean they are of importance for human brain research.
- Without action, the knowledge base behind these compounds and their potential for use in human studies will soon be lost for good.
- ECNP has implemented the Medicines Chest Initiative to preserve important compounds.
 - Consultation with members
 - Identification of target compounds
 - Website



Vision

- The medicines chest will serve as the guardian and data repository
 - pharmacological tools acting at key brain receptors and enzymes
 - live data packages that will support human studies.
- There will be access to these agents for use in human experimental medicine studies by *bona fide* researchers.
- Data generated from studies with compounds in the medicines chest will be made publically available.
- It will become normal practice for pharmaceutical companies to contribute any shelved CNS-acting compounds to the medicines chest.

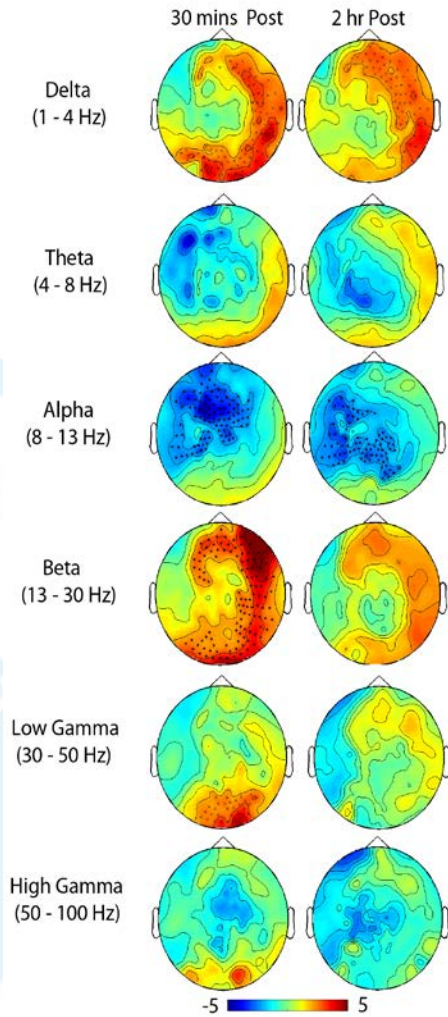


Example - Gaboxadol

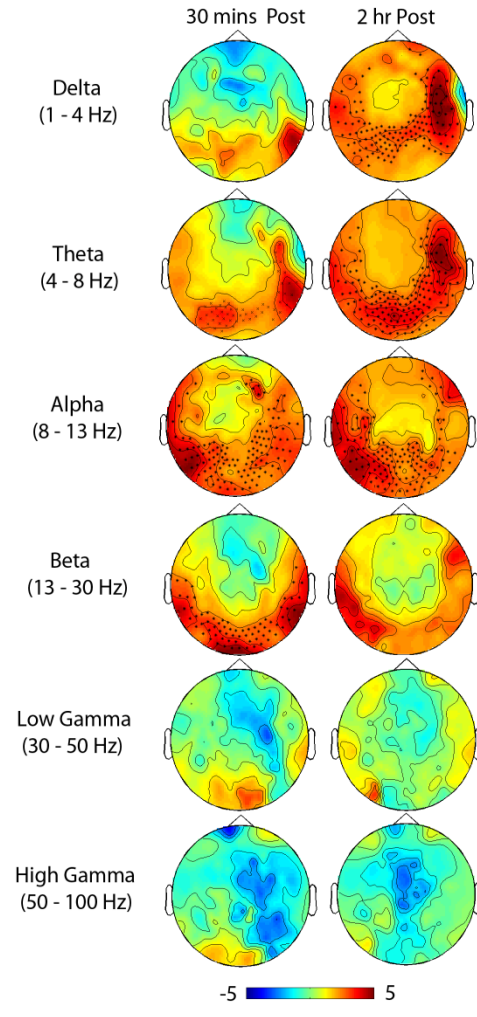
- Gaboxadol is the first compound to enter the medicines chest, in partnership with Lundbeck.
- The compound was in development as a novel treatment for insomnia and reached Phase III clinical trials.
- After development was halted, Lundbeck provided relevant safety data to support a human study and drug product.
- The first study has now been completed using magnetoencephalography to measure effects on brain neuronal activity.
- This showed a very distinct psychopharmacological profile for the extra-synaptic agent that is fundamentally different from that of intra-synaptically acting GABA_A hypnotics such as zolpidem.



Zolpidem



Gaboxadol





Target List

- 5-HT_{2A} receptor antagonist
- Dopamine D₁ receptor antagonist
- Nicotinic α_7 receptor agonist
- GABA_A receptor α_5 inverse agonist
- GABA_A receptor $\alpha_{2/3}$ positive allosteric modulator
- Translocator protein (TSPO) agonist
- Glycine transporter 1 (GlyT-1) inhibitor
- Cannabinoid CB₁ receptor antagonist or inverse agonist
- Cannabinoid CB_{1/2} receptor agonist
- Fatty acid amide hydrolase (FAAH) antagonist



Status

- Discussions with 17 pharmaceutical companies regarding 30+ compounds
 - Generally supportive
 - See ‘good citizen’ role
 - Other compounds not on original target list offered
 - Sometimes difficult to overcome inertia and find the right person
 - More difficult with smaller companies due to resource issues
 - Many companies undergoing reorganisation currently
- Other organisations
 - EFPIA
 - ABPI
 - MRC



Compounds 1

In the chest	Gaboxadol (extra synaptic GABA agonist)	
	Idazoxan (α_2 antagonist/imidazoline antagonist)	
	Emapunil (TSPO agonist)	✓
Probables	5-HT _{2A} antagonist	✓
	GABA _A $\alpha_{2/3}$ positive allosteric modulator	✓
	Histamine H ₃ inverse agonist	
	Dopamine D ₁ antagonist	✓
	CRF ₁ receptor antagonist	
	5-HT ₇ receptor antagonist	
	Nicotinic α_7 receptor antagonist	✓

✓ = on original target list



Compounds 2

Possibles	5-HT _{2B} antagonist	
	GABA _B antagonist	
	CB ₁ antagonist	✓

✓ = on original target list



Compounds 3

Not available currently	Rimonabant	CB ₁ inverse agonist	✓
	GSK2182883	Nicotinic alpha ₇ agonist	✓
	Adrogolide (ABT-431, DAS-431)	Dopamine D ₁ agonist	
	a5IA	GABA _A alpha ₅ inverse agonist	✓
	L838417	GABA _A alpha _{2/3} positive allosteric modulator	✓
	Org 25935	GlyT-1 inhibitor	✓
	Org 28611	CB _{1/2} agonist	✓
	Org 28312	CB _{1/2} agonist	✓
	Org 50189	CB ₁ antagonist	✓
	GSK598809	Dopamine D ₃ antagonist	
	URB597, PF-622, PF-750, PF-3845	FAAH antagonist	✓

✓ = on original target list



Contracts

- Two templates available
- Several companies have agreed a contract with NIH for NCATS – an adapted version of this may be a convenient route



Next steps

- Finalise agreements on the new additions to the medicines chest
- Establish a secure, well managed, repository of data for compounds in the medicines chest
- Maintain live investigator's brochures (and other regulatory documentation)
- Maintain usable cGMP drug substance and drug product (and placebo)
- Attract and facilitate high quality study proposals employing the tools in the chest via the ECNP
- Continue to add new compounds