Recent advances in the management of schizophrenia

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Declaration of interests

- Advisory board fees Abbvie, Janssen-Cilag.
- Research funding MRC, EU, NIHR
- Spin out company Affigo CiC.
Schizophrenia

• Onset in early adult life
• Psychotic illness with positive and negative symptoms, plus cognitive impairments
• 1 in 200 people
• Direct costs of health and social care in UK: £3 billion.
• Life expectancy reduced by 17 years
Outcome in schizophrenia

• 80% will recover from first episode, usually within 3 months
  – BUT
• Relapse in 30% by one year; 80% by 5 years
• Negative symptoms often persist
• Suicide in 5%
Three sorts of intervention

• Drug treatments
• Psychological treatments
• Service-level interventions
How to tell what works

• Randomised controlled trials
  – Difficult and expensive to do well
Drug treatments
The Dopamine Hypothesis

Schizophrenia is the result of increased dopaminergic function in certain brain areas:

*EITHER* from disruption at predominantly *post-synaptic* sites; e.g. increased post-synaptic receptor numbers

*OR* from disruption at predominantly *pre-synaptic* sites; e.g. increased absolute levels/tturnover
The Dopamine Hypothesis

Schizophrenia is the result of increased dopaminergic function in certain brain areas:

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*OR* from disruption at predominantly pre-synaptic sites; e.g. increased absolute levels/turnover
So why do antipsychotic drugs take 2-4 weeks to start working?
Early versus delayed acute drug action

Agid, Kapur et al 2003
Early antipsychotic response

• Ziprasadone IM double blind vs placebo: PANSS positive subscale score at 4 hours $p<0.05$ (Agid et al, 2008)

• 30% reduction in PANSS total at 2 weeks best predicts 6 week outcome (PPV 70%; NPV 80%)

• Patients with no or minimal improvement of symptoms during the first week of treatment are unlikely to respond to a 4 week trial
SGAs: the perceived advantages

• Increased efficacy
  – Positive symptoms
  – Negative symptoms
  – Mood symptoms
  – Cognitive deficits

• Fewer side effects

• Better functional outcomes

• Cost effective
FGA vs SGA prescriptions primary care England 1993-2010
Postcode prescribing: clozapine Greater Manchester 1996-2011

Population & Need Adjusted Data

# of Prescriptions

- Tameside
- Rochdale
- North Manchester
- Central Manchester
- South Manchester
- Trafford
- Bolton
- Bury
- Oldham
- Salford
- Stockport

- 1996
- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
Hypothesis of 5 point advantage for SGA
Hypothesis of 5 point advantage for SGA excluded
Schizophrenia patients do as well, or perhaps even better, on older psychiatric drugs compared with newer and far costlier medications, according to a study published yesterday that overturns conventional wisdom about antipsychotic drugs, which cost the United States $10 billion a year. The results are causing consternation. The researchers who conducted the trial were so certain they would find exactly the opposite that they went back to make sure the research data had not been recorded backward.

The study, funded by the British government, is the first to compare treatment results from a broad range of older antipsychotic drugs against results from newer ones. The study was requested by Britain's National Health Service to determine whether the newer drugs -- which can cost 10 times as much as the older ones -- are worth the difference in price.
Highlights of Phase I

• High rate of discontinuation (switching)
  – Hypothesized 60%
  – Consistent with practice and clinical trials
• OLZ most effective
  – Best efficacy, worst side effects
• PER comparably effective to SGAs
  – Slightly higher EPS
• No differential effects of SGAs on Sxs including negative Sxs
  – Cognition, substance abuse, violence
• Differences in types and severity of side effects
• Consistent results across multiple measures within domains
• Full dose range not explored before switching
CATIE and CUtLASS

• Same rationale
• Different design
• Same conclusions:
  – No clear advantage of SGAs over FGAs in effectiveness, safety or costs for people with chronic schizophrenia.
  – Clozapine better than other SGAs.
Greater Manchester PCTs - Weighted prescribing cost of 'typical antipsychotics' since January 2007:

(All)

<table>
<thead>
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<th>Act Cost/1000 patients</th>
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<tr>
<td>Ashton, Leigh &amp; Wigan</td>
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<td>Bolton</td>
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<td>England</td>
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But surely SGAs are the treatment of choice in first episode psychosis?
Response rates in 6-12 week double blind first episode trials

- Emsley 99
- Lieberman 03
- Schooler 05
- Moller 08
- Lieberman 03b

Drugs:
- risperidone
- haloperidol
- olanzapine
- chlorpromazine
- clozapine
Are SGAs better for your brain?
Total grey matter volume change over one year after first episode psychosis and antipsychotic drug load

This correlation was evident even when controlling for poor clinical outcomes.

Cahn et al 2002
Do antipsychotic drugs damage your brain?

Dorph-Petersen et al (2005)

18 macaque monkeys assigned to 2 year course of placebo, haloperidol or olanzapine at doses equivalent to therapeutic human doses

Brain volume change at 2 years:

- Placebo: 0%
- Haloperidol: -8.8%
- Olanzapine: -10.5%

p<0.05 for both drugs
Depot (long acting) medication

- About 35% of people with schizophrenia will receive LAI medication
- SGA LAIs (risperdal consta, paliperidone) now widely used but expensive, and no strong evidence that they are better than FGA LAIs
- CUtLASS 1: what participants were randomised FROM (43% on LAI at baseline) more important for outcome than what they were randomised TO (FGA vs SGA; Barnes et al, BJP 2013).
LAI in first episode

Open rct of risperidone LAI versus oral risperidone in 57 people with first episode schizophrenia over 1 year

- Relapse: 5% vs 32%
- Hospitalisation: 5% vs 18%
- All cause discontinuation: 12% vs 33%
- Perfect adherence: 73% vs 7%
- Improved working memory, visual learning (MCCB)
- Better work outcomes

Nuecheterlein et al in press
New drugs: an uncertain future

• Pomaglutamad (Lilly)
  – Metabotropic glutamate m2/3 receptor agonist
  – Phase 2 trials successful; phase 3 failed (post hoc – signal in early psychosis, Kinon et al 2014)
• Bitopertin (Roche)
  – Glycine reuptake inhibitor adjunct for negative Sx
  – Phase 2 trials successful; 5 of 6 phase 3 trials failed
• α7 nicotinic receptor agonists (Abbvie and others)
  – Improve cognitive impairment
  – Positive phase 2 results but probably not proceeding
Psychological treatments
CBT Effect Size by trial quality
CBT Effect Size by trial quality

The chart shows the effect size of CBT across different trial qualities. The x-axis represents the trials, numbered from 1 to 19, and the y-axis represents the effect size ranging from -0.6 to 1.0. The bars indicate the effect size for each trial, with some trials showing a significant effect size compared to others.
SoCRaTES trial

• Independently rated as highest quality CBT/psychosis trial. MRC-funded trial of brief 6-week CBT vs supportive counselling vs usual care in n=308 acute 1st/2nd episode clients.

• Results
  – CBT accelerates improvement in acute symptoms
  – leads to improved outcomes at 18 months
  – effects small, but measurable and durable
  – BUT SO DID SUPPORTIVE COUNSELLING

All psychological treatments work

• So-called Dodo bird hypothesis
  – “everyone’s won and all must have prizes!”
• Supportive counselling as good as CBT
• BUT what drives this effect might be the therapeutic alliance: “the quality of the relationship between therapist and client, characterised by trust and a sense of common purpose”.
• How to prove this?
SoCRaTES trial

- Therapeutic alliance rated by therapist (Frank and Gunderson scale) and client (CALPAS scale).

- CALPAS showed
  - With a good TA, attending more sessions causes a significantly better outcome on PANSS total score (effect size -2.91, 95% confidence interval -0.90 to -4.91)
  - With a poor TA, attending more sessions is detrimental (effect size +7.74, 95% confidence interval +1.03 to +14.45).

- No-one has shown this before.

Lucy Goldstein et al 2014
Service redesign
- through connected health
m-Health for people with psychosis

www.clintouch.com
How it works

Queries

Responses

Real-time information gathering
ClinTouch/Careloop

• Careloop

  – Aim: an end-to-end solution linking client and professional in the co-production of care.

  ➢ Customisable, secure interface for clinical teams
  ➢ Real-time data summaries streamed to team base, ECRs
  ➢ Personalised relapse signature/EWS triggers alert at team base.
## Four impacts

<table>
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<tr>
<th>Improved user experience of care</th>
<th>User health self-management</th>
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<td>Early intervention and prevention</td>
<td>Research capability</td>
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People with SMI: opinions of health professionals 2010

They said

- Few users own and use a mobile
- Users won’t be interested
- They’ll lose or sell the handset
- It will make users paranoid
- It will be too complicated
- It will take too long to complete
- They will stop using it
- Responses might be made up
- Responses won’t resemble interview data

We found

- 85% do.
- 80% of those approached agreed
- 1/44 lost handset
- 2/44 discontinued for this reason
- 36/44 completed >33% of 36
- Average 70 seconds
- 81% completed a week
- Not the case.
- Very high correlations on key items
How it works
How it works

Beep
How it works

- Beep
- Respond
How it works

Beep

Feedback

Respond
How it works

- Beep
- Feedback
- Respond
- Share
- Thresholds
- Show
- Mental health team
- Careloop
- Health professional
- Family/friends
Correlations with gold standard interviews

- Hopelessness: 0.80*
- Delusions: 0.74*
- Anxiety: 0.69*
- Hallucinations: 0.68*
- Suspiciousness: 0.63*
- Grandiosity: 0.53*
- Depression: 0.45*
- Guilt: 0.44*
- Somatic concern: 0.39*
- Social withdrawal: 0.26
- Hostility: 0.25
- Excitement: 0.06
- Disorganisation: -0.04

*p < .05
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Experience-based design

Service user advisory group:
Dawn Perry, Jamaal Hatton, Neal Sinclair, George, Kate Lurie, Deborah Peer

https://www.facebook.com/MakingMentalHealthPositive

- Advice on study information, design of methods, focus group topics and questions, feedback/suggestions for app design changes. Barriers to adoption.
- Focus groups: 23 SMI users, 5 carers, 30 staff

EBD is a user-focused design process with the goal of making user experience accessible to the designers. (Bate & Robert, 2006)
The nice thing about it, it’s not taking a tablet…it’s just using a phone.

Yeah. Because every time I see my care coordinator for some reason I’m all right. She says: what have you done for two weeks? And I don’t remember...

Some people... they’ll do it twice a day. The person who’s doing it, it’s up to them. It’s our illness.

Users: collaboration and flexibility

The idea of linking up with somebody that’s on my level – just similar – that would be perfect. Like... a virtual drop in.

...Maybe in the morning or maybe in the evening, but the idea of filling it in in front of other people and trying to explain to other people what it’s about, it’d attract attention.
Personalisation and usability

Remember how good you feel when you go for a run

www.keepitusable.com
ClinTouch/CareLoop

• Feasibility
  – 181 with DSM5 psychotic disorders eligible; 81 (46%) consented
  – 38/40 randomised to ClinTouch completed 12 weeks’ monitoring
  – Adherence over 12 weeks:
    • 60% of participants >50% response rate to item set 4x per day
    • 84% of participants >33% response rate.

• Health professional use of system
  • 100% of care coordinators accessed the system at least once over 12 weeks, with a mean of 24 times.
ClinTouch/CareLoop

- Efficacy on primary outcomes ClinTouch vs standard care:
  - **PANSS total** (assessed 6 and 12 weeks), **PANSS positive**
    - ANCOVA NS across two centres
    - BUT predicted interaction by centre p<0.01 of early intervention (EI) site (n=44, mean age 26y) vs community team site (n=37, mean age 46y).
    - EI site: **PANSS total** adjusted mean benefit of 6 points (p=0.08, 2 tailed). **PANSS positive** AMB of 3 points (p=0.02).
  - **Empowerment Rating Scale** score NS
    - BUT exit qualitative interviews suggested improved self management skills
ClinTouch/Careloop

- Efficiency in detecting early warning signs of relapse
  - ClinTouch personalised alerts to clinical team desktop compared to blindly rated episodes of EWS from electronic care records (ECR) over 12 weeks
  - ClinTouch alerts in 88% of cases vs 33% of cases as recorded in ECR (cf 43% in standard care ECRs).
  - Sensitivity 75%, specificity 8%
  - BUT further analyses form the basis for adjusting ClinTouch alert criteria to improve ROC curve eg specifying minimum duration of alerts.
www.clintouch.com

@clin_touch
An example: temporal association between metacognition and auditory hallucinations
That’s all, folks!
Clintouch/Careloop

- **Clintouch**
  - Development funded by 3 MRC grants
  - Commodity mobile phone technology, using existing device, so minimal lifestyle intrusion. Familiar operability and interface.
  - Safety assessed first
  - Generalisable: 80% of SMI clients own and use mobile phones
  - Acceptable: (short term at least): 81% compliant
  - Personalisable; modular, with machine learning of responses
  - Clinical data shown to be valid
  - Platform technology for monitoring and interventions across long term conditions

- **Careloop**
  - provides an end to end solution linking client and professional in the co-production of care
Recent and next steps

• Attachable modules
  – Medication management support, side effects monitoring: Optimise trial
  – Contextual assessment
  – Social networking: “virtual drop in”
  – CBT support
  – Biosensors: sleep and exercise sensors; mood recognition
  – Neurocognition
  – Ecologically-valid functional assessment
LAIs in first episode

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Nuecheterlein et al in press
www.clintouch.com
CUtLASS 3?

- Risperidone LAI
  - Since 2002
  - 50mg 2 weekly £4000 pa
  - High wastage
  - Manchester MHSCTrust spend Consta £560k 08/09
  - Depixol 40mg monthly £90
  - No evidence for better effectiveness/ tolerability
  - Paliperidone, olanzapine LAIs due 2011