Update on management of anxiety and depression

CHIDAMBARAM PRAKASH
AUTHORISED PSYCHIATRIST
ROYAL CHILDREN’S HOSPITAL MELBOURNE
General principles of pharmacotherapy

- History: 1937: Charles Bradley, Molich & Eccles used benzedrine to treat ‘ADD’
- Children need higher weight adjusted doses
- Developmental changes affect Dopaminergic (> dystonia), Serotonnergic (> activation symptoms) & Noradrenergic systems (tricyclics less effective in depression)
ANXIETY DISORDERS
Anxiety & OCD prevalence

- 4%-9% lifetime prevalence in children
- The risk of developing an anxiety disorder in children between the ages of 7–17 years is three times as high if a parent has/had an anxiety disorder compared with other diagnoses.
- The lifetime prevalence of OCD was significantly higher in case compared with control relatives (11.7% vs 2.7%)
- The first-degree relatives of probands diagnosed with OCD had a more than 5-fold higher lifetime prevalence of OCD.
Neural circuitry in anxiety

- Cortex to Amygdala to Thalamus to prefrontal cortex
- The failure of the prefrontal cortex to curb the over excitability of the amygdala causes anxiety symptoms
- Amygdala & Hippocampus closely connected leading to laying down of (trauma) memories
‘Normal’ Anxiety-AS temporary states

- More catastrophic thinking (Davey)
- Poorer performance on problem solving tasks due to reduced concentration (Dugas)
- Avoidance, intolerance of ambiguity, elevated evidence requirements (Davey, Freeston, Tallis)
- Anxious people are high worriers: Can be self conscious, self evasive, perfectionistic, time pressured, obsessional
Why Worry?

- Based on verbal-linguistic-cognitive system
- Problem solving
- Planning the process of coping
- Because its verbal, reduced emotional reprocessing. This is good & bad.
- But maintains pathological worrying
- Cognitive avoidance
- Sensitisation to future problems
DSM 5 What's new?

- **Panic Attack**
  - “unexpected” / “expected” panic attacks.
  - Panic attacks occur with a range of disorders

- **Panic Disorder and Agoraphobia**
  - Divorced, each with separate criteria.
  - Agoraphobia now requires also fears from two agoraphobia situations.
**Specific Phobia**
- Removal of the requirement that persons over the age of 18 yrs. must recognise their anxiety and fear is excessive or unreasonable.
- The duration requirement now applies to all ages (“typically lasting > 6 months”).

**Social Anxiety Disorder (Social Phobia)**
- “performance only” specifier
DSM 5 What's new?

- **Separation Anxiety Disorder**
  - An anxiety disorder.
  - Now includes Separation Anxiety Disorder in adulthood.
  - The criterion that onset must be before the age of 18 yrs. has been removed.

- **Selective Mutism**
  - This is also now classified as an Anxiety Disorder, given that a large majority of the children with selective mutism are anxious.
Impact of changes?

Well, it depends on who has the loudest voice....

...............and who’s paying.
Clinician ratings of the usefulness of the DSM-5 approach compared with the DSM-IV approach for selected disorders of pediatric patients.

Overall, how would you compare the usefulness of the DSM-5 approach (i.e., the use of information from the cross-cutting measures, diagnostic criteria, and the diagnostic-specific severity measures) to the DSM-IV approach to the diagnosis?

- Much better
- Better
- About the same
- Worse
- Much worse

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<th>Disorder</th>
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Level of Evidence Favouring Efficacy of Psychosocial Treatment

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<th>Treatment Type</th>
<th>OCD</th>
<th>PTSD</th>
<th>PDAG</th>
<th>SAD</th>
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# Level of Evidence Favoring Efficacy of Drug Treatment

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<th>Condition</th>
<th>TCA</th>
<th>SSRI</th>
<th>BZD</th>
<th>?2-Agonist</th>
<th>5HT1A Agonist</th>
<th>Heterocyclic</th>
<th>1Clomipramine only; 2Mixed results; 3RUPP study of SAD, GAD social phobia; 4May induce disinhibition; 5 I = Likely ineffective; 6No data on which to base conclusion</th>
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### Studies in using SSRIs in non OCD conditions
#### Dec 2011 review

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<th>Study</th>
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<th>Dosing</th>
<th>Length (mg)</th>
<th>Conditions</th>
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<td>RUPP Anxiety Study Group, 2001</td>
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<td>Black &amp; Uhde, 1994</td>
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<td>Walkup et al, 2008 [12]</td>
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<td>March et al, 2007 [50]</td>
<td>Venlafaxine ER (VFX)</td>
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<td>Weight-based flexible, (141 5mg)</td>
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<td>8-17 SoP</td>
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<tr>
<td>Rynn et al, 2007 [49] (pooled studies)</td>
<td>Venlafaxine ER (VFX)</td>
<td>8</td>
<td>Weight-based, flexible.</td>
<td>320</td>
<td>6-17 GAD</td>
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**OCD**

- Prepubescent children-CBT first
- Adolescents-CBT for milder OCD, CBT+ SRI for severe OCD
- POTS (Franklin 2011): Sertraline with CBT.
- FDA approved: Sertraline (Wagner, March, Manassis) Fluoxetine (Riddle, Leibowitz) & Fluvoxamine (Riddle)
- SRI: Get to minimum effective dose in 12 weeks and stay. If inadequate response then push higher to max and try for 4-6 weeks (Esser 2012, Geller 2006)
- Pushing up dose gradually better than front loading in getting better effects (Lee, Esser 2010)
Treatments-OCD

- If inadequate response to CBT or SSRI alone then combine (POTS study 2011)
- If inadequate response to combination then switch SSRI
- After 2-3 trials of SSRI +CBT then Clomipramine
- If still no response then augment with another medication (depending on symptom)
- Maintenance: after 3-4 mild relapses or 2-3 severe relapses
- Gradually taper over 1-2 years-reduce by 25% wait for 2 months before next decrease. Continue monthly CBT
Dosing in OCD-Rappaport 2011

- Fluoxetine up to 80-100 milligrams
- Sertraline up to 200 milligrams
- Fluvoxamine up to 150 milligrams
22 short-term (<= 16 weeks) RCTs were included in the analysis (2519 participants). The majority of the trials assessed the efficacy of the SSRIs (N = 15). Medication and placebo response occurred in 58.1% and 31.5% of patients,

- SSRIs can be effective in paediatric anxiety disorders, acting to reduce core symptoms, and should be considered as part of the treatment of these disorders.
- The greatest number of trials showing efficacy to date have assessed the SSRIs in treating paediatric OCD.
- There is no clear evidence to show that any particular class of medication is more effective or better tolerated than any other.
- As quantitative data was only available for the SSRIs and venlafaxine the routine use of benzodiazepines cannot be recommended,
DEPRESSION
Depressive disorders prevalence

MAJOR DEPRESSION
- Pre-schoolers: 0.3% (community), 0.9% (clinic)
- School age: 2% Boys>Girls
- Adolescents: 5% (community), 20-40% (patients in psych Hospital)
- Depressive sx 14 –62%, Duration: 26 –36 wks Girls>Boys
- MZ: 50% concordance and DZ: 20%

DYSTHYMIA
- School age: 2.5% Adolescents: 3.3% Boys=Girls
Figure 3.1. Factors affecting vulnerability to depression in adolescence.
Individual Predisposition
- Alcohol abuse
- Depression
- Character Disorder
  - aggressive/impulsive
  - perfectionistic/rigid

Proximate (Trigger)
- Stress Event
- Altered state of mind
  - hopelessness
  - fear/dread, rage etc
- Opportunity: available method, privacy etc

Social Milieu
- High or Low community rates
- Taboos
- Media Display

Inhibit or facilitate

Case finding and treatment

Hotlines

Firearm education

Preventions

Media Guidance
Enhance Taboos

SUICIDE
Australia 1997: Suicide - Comparisons with 23 other Countries

Age Groups

- 75 +: 15
- 65 - 74: 13
- 55 - 64: 15
- 45 - 54: 13
- 35 - 44: 13
- 25 - 34: 8
- 15 - 24: 4

Ranking
# Neurotransmitter Deficiency Hypotheses of Depression

- Serotonin
- Norepinephrine
- Dopamine
- Gamma-aminobutyric acid (GABA)
- Brain-derived neurotrophic factor (BDNF)
- Somatostatin
Assessing Risk
4 Rs

- Recognising the signs
- Raising the issue
- Risk Assessment
- Responding
Establish Rapport

- Non Judgmental
- Unhurried
- Active listening
- Confidentiality issues
- Individual Assessment
- Family involvement
- Make some positive comments
Recognising the signs: Antecedents

- Depression
- Self harm
- Substance abuse
- Recent Loss
- Antisocial Aggressive behaviour possession of a firearm.
Recognising the signs: Behaviours

- Numerous Accidents
- Dangerous Risky Behaviours
- Morbid thoughts
- Giving away favoured possessions
Other Risk Factors

- Psychiatric disorders
- Poor social adjustment
- Physical health problems
- Family and Environmental Factors
Factors that impede disclosure

- Clinician not prepared
- Anxiety / fear about mismanagement
- Anger with repeated self harmers
- Denial of possibility of suicide because of personal views
1. Have you been feeling depressed for several days at a time?

3. When did these thoughts occur?

5. Did you act on these thoughts in any way?

7. When was the last time you had these thoughts?
Assessing Suicide Risk: 2

9. Recently, what specifically have you thought about doing to yourself?

11. Have you thought about when and where you would do this?
13. Have you thought about the effect your death would have upon your family or friends?

15. What are your thoughts about staying alive?

17. How does talking about all this make you feel?
Attempted Suicide

Risk Factors

- Male gender
- Poor Communication
- History of Previous Attempts
- Depressive Symptoms
- Sense of Hopelessness
- Persistent Suicidal Ideation
Suicide and Attempted Suicide

- Psychopathology: psychiatric disorder common amongst suicides
- High rates of behaviour disorder
- High rates of Substance abuse especially amongst males
- Parent - Adolescent Communication less good in suicides
Attempted Suicide

- **Suicidal ideation**: 27% thought of suicide in the last 12 mths;
  16% had made a plan;
  8% had made an attempt;
  2% an attempt which required medical attention

- **Lethal Intent**: 70% certainly survivable, 26% lethal potential, 4% death a distinct possibility

- **Females** more likely to attempt suicide than males
  (but less so as ascertained by community samples)

- **Low SES** associated with suicide attempts
Attempted Suicide

- F:M = 6:1
- Usually only return for a few sessions therefore brief intervention strategies are important
- Cognitive problem solving strategies
- Identify potentially stressful situations
- Improve family communications and support, reduce conflictual situations
Attempted Suicide

- **Attempters**: low rates of affective disorders, high rates of Disruptive disorders, and substances abuse
- **Cognitive Factors**: sense of hopelessness; poor problem solving strategies, negative attributional style, impulsive style
- **Outcome**: 50% will repeat attempts within the first 2 yr... 10% (approx.) will complete suicide
DEVELOPING A MANAGEMENT PLAN

1. Establish a Therapeutic Alliance
2. Be systematic in your assessment
3. Where feasible, remove all obvious means of self harm.
4. Ensure appropriate supervision for the individual
5. Ensure immediate 24 hour access to suitable clinical care
6. Where feasible, neutralise the precipitating problem
7. Try to make a contract to keep themselves safe
8. Try to delay the individuals suicidal impulses: offer strategies
9. Identify supportive people or services who can be contacted
10. Engage in ongoing consultation with colleagues
Neurotransmitter Excess Hypotheses of Depression

- Acetylcholine
- Substance P
- Corticotrophin Releasing Hormone (CRH)
Serotonin in Major Depression

- Cerebrospinal Fluid
- Neuroendocrine challenges
- Platelets
- Postmortem brain
- Depletion
- Imaging
- Genes
Serotonin Function is Abnormal Between and During Episodes of Major Depression

- May explain why 80% of patients have recurrences of major depressive episodes.
- May explain why prevention of relapse back into an episode and prevention of future episodes requires ongoing medication.
ANTIDEPRESSANT ACTION

- Enhance serotonin function by SSRI, MAOI, lithium or tricyclic antidepressant medication.
- Enhance norepinephrine or dopamine function by NERI or MAOI.
- Increased receptor number induced by ECT or enhance signal by second messenger effects.
- Enhance GABA function (anticonvulsants).
- Infuse BDNF intrathecally (serotonin growth).
WHY IS THERE A DELAYED ONSET OF ACTION of ANTIDEPRESSANTS

- SSRIs cause gradual desensitization of 5-HT1A autoreceptors without change in 5-HT1A postsynaptic terminal field receptors, gradually amplifying the serotonin signal.
- ECS causes progressive postsynaptic 5-HT1A receptor upregulation, without effect on autoreceptors.
The full list of tried and tested Psychological therapies for Depression

- Child, Parent Psycho education
- Cognitive/Coping
- Problem Solving
- Activity Scheduling
- Skill-building/Behavioral Rehearsal
- Social Skills Training
- Communication Skills
- Interpersonal therapy
- Dialectical Behavior therapy
A group cognitive behaviour therapy (CBT) programme for preventing depression, delivered universally in a school setting, may not reduce symptoms of depression in young people at high risk of depression, and could increase reporting of symptoms.

- Computerised CBT may be a valid treatment option for young people with mild depression.
Moderate to severe depression

- Combining CBT and newer antidepressants may bring some limited benefits in the short term over either therapy alone, particularly with regard to global functioning.
- When medication is used for children and young people, fluoxetine is the antidepressant of choice, because it is the only antidepressant licensed for this use in the USA—Fluoxetine and Escitalopram. There remains little evidence to inform views on the relative value of other antidepressants.
Published double-blind, placebo-controlled studies: SSRI efficacy for MDD

- Studies in children & adolescents:
  - Emslie et al (1997): modest fluoxetine efficacy: fluoxetine 58%, placebo 32%
  - Keller et al (2001): paroxetine efficacy: paroxetine 63%, imipramine 50%, placebo 46%, 1 of 2 primary outcome measures was significant; 2 other studies were negative
  - Emslie et al (2002): fluoxetine efficacy: effects modest (fluoxetine 41%, placebo 20%) & not all outcome measures were significantly different than placebo
FDA Review of Studies for Antidepressant Drugs

- 20 placebo-controlled studies of 4100 pediatric patients for 8 antidepressant drugs (citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine)
- Excess of suicidal ideation & suicide attempts when receiving certain antidepressant drugs; no suicides
- FDA could not rule out an increased risk of suicidality for any of these medications
- Data was adequate to establish effectiveness in MDD only for fluoxetine based on 2 studies (by Emslie et al)
More reviews of studies (RCTs)
Courtney et al (04), Jureidini et al (05), Birmaher (96)
Garland (04)

- Weak evidence for efficacy, inconclusive for safety even for Fluoxetine
- Improvement in placebo groups.
- Not one study adequately examines safety
- Non standardized data collection for adverse effects
- Exclusion of suicidal subjects, small sample sizes, conflict of interest, unpublished data
- Feasible treatments by GPs for milder cases (Gledhill 2003)
Actual evidence for anti-depressants in kids (Whittington et al 2004)

- Published & Unpublished data
- Risk vs benefit evidence
- Some positive evidence for Fluoxetine
- Weak positive evidence for Sertraline
- Negative evidence for Paroxetine, Venlafaxine & Citalopram.
- Lack of openness in publishing data
Figure 1. FDA-Approved Pediatric Age Ranges and Indications for Antidepressant Medications

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- **ch**ildhood **e**nuresis
- **MDD**
- **OCD**

*Fluoxetine is FDA approved for the treatment of MDD in pediatric patients up to 18 years old.*
Depression-TADS-Kennard 2009

- 459 Depressed adolescents
- 12-17 years, 54.4% girls 73.8% white, 12.5% African-American, 8.9% Hispanic
- Co morbid: GAD, ADHD, ODD, Social Phobia, Dysthymia
- Fluoxetine, CBT, Combo & Placebo
- Acute phase: 0-12 weeks, Continuation: 12-18, Maintainence 18-36.
- At 36 weeks combo was better than either alone, CBT slightly better than FLX
- Majority of patients remitted by 9 months
334 initial SSRI treatment resistant depressed teenagers (12-18 years) randomized to another SSRI (fluoxetine, citalopram, paroxetine), Venlafaxine with or without CBT.

- Most patients (2/3) remitted at 24 weeks but ¼ remitters relapsed
- Best response to SSRI+CBT
- NSSI & CSA worsened chance of suicide attempts
- Those with a h/o physical response responded poorly to SSRI + CBT treatment
Treatment of MDD: Tricyclic Antidepressants (TCA’s)

- TCA’s: imipramine, desipramine, amitriptyline, nortriptyline, doxepin
- Tricyclic antidepressants (TCA’s) have 50%-60% response rate for MDD; but studies limited by sample size, duration of treatment, dose of TCA’s, inclusion of patients with mild MDD
- Findings suggest that TCA’s have little benefit in children & adolescents
Other relevant studies

- Showed that adolescents can benefit from Fluoxetine even in mild to moderate depression (Gibbons 2012).
- Same review shows that all SSRIs are now equal in suicide risk. SSRIs reduce factors behind suicide risk such as NSSI, depressed mood and does not directly increase risk of completed suicide.
Cardiac toxicity of Citalopram & Escitalopram

- Mohammed et al Dec 2010: OD with Escitalopram (15-20 tabs) with Lithium (15-20 tabs of 300 mgs)
- Fayssoil Et al Jan 2011: Single case report of Long QTc with Citalopram taken with Amiodarone
- Liotter Oct 2011: OD with Citalopram caused long QTc
- Howland et al Nov 2011: Not enough clinically significant evidence to justify FDA caution
- Yager et al May 2013: 1.1% of patients receiving citalopram or sertraline experienced ventricular arrhythmias. Cardiac deaths occurred in 3.3% of citalopram recipients and 4.0% of sertraline recipients
Duloxetine (Cymbalta)-SNRI-effective for depression and pain
- Half life is 12 hours so requires twice daily dosing
- Dose: 30 -120 mg a day
- Deemed safe for use in children and teenagers (7-17 years). Possibly efficacious (Burkhart 2012)
- Useful in treating ADHD in teenagers (Mahmoudi Gharei et al 2011). Improvements noted in 5 weeks
Duloxetine vs Fluoxetine

- Double blind study by Emslie et al 2014.
- **Methods:** Patients ($n=463$) in this 36 week study (10 week acute and 26 week extension treatment) received *duloxetine 60 mg* QD ($n=108$), *duloxetine 30 mg* QD ($n=116$), *fluoxetine 20 mg* QD ($n=117$, active control), or placebo ($n=122$). Measures included: Children's Depression Rating Scale-Revised (CDRS-R), treatment-emergent adverse events (TEAEs), and Columbia-Suicide Severity Rating Scale (C-SSRS).
Duloxetine vs Fluoxetine

- Adverse effects: more than placebo for Duloxetine 60 mg
- A total of 7 (6.7%) duloxetine 60 mg, 6 (5.2%) duloxetine 30 mg, 9 (8.0%) fluoxetine, and 11 (9.4%) placebo patients had worsening of suicidal ideation from baseline during acute treatment.
- Of the patients with suicidal ideation at baseline, 13/16 (81%) duloxetine 60 mg, 16/17 (94%) duloxetine 30 mg, 11/16 (69%) fluoxetine, and 13/15 (87%) placebo had improvement in suicidal ideation at end-point during acute treatment (10 weeks).
- One fluoxetine, one placebo, and six duloxetine patients had treatment-emergent suicidal behaviour during the 36 week study.
Newer antidepressants

Desvenlafaxine- Prestig SNRI

- 50-200 mg once daily dose
- Gradual withdrawal may be required to prevent discontinuation syndrome
- Main side effect is nausea
- Double blind placebo controlled studies underway
New antidepressant

- Vortioxetine: So-called "serotonin modulator and stimulator, atypical antidepressant
- Reportedly acts very quickly
- No child studies
Agomelatine superior to Fluoxetine Hale et al 2010 Oct

- Agomelatine (25-50 mgs) MT1/MT2 receptor agonist, 5 HT2C antagonist was studied in >200 patients vs Fluoxetine
- Agomelatine was found to improve depressive symptoms whilst having fewer adverse effects & improving sleep
- Strengths: 25 and 50 mg.
- Liver function monitoring needed
GLYX-13 (MOSKAL 2013)

- New antidepressant that works on the Glutamate and NMDA receptor system
- Supposed to work within 24 hours with twice the effect size of current ADs 4-6 weeks.
- Far fewer adverse effects than current ADs
Younger adolescents with depression show overactivity to fearful stimuli in amygdala, orbitofrontal cortex, subgenual anterior cingulate cortex.

Fluoxetine reverses this.

Adults & older adolescents (16 years) show underactivity in these regions during depression but Fluoxetine does not make any changes, still improves symptoms.
Do SSRIs cause suicidal behaviour in teenagers?
Prescribing trends

Gibbons (2005)

- Increased use in Australia, US (Zito), UK (Phillips, Murray), Italy, Sweden etc. But lower rates of suicides.
- Japan- Increased use and suicides but cult reasons


- 1.6% to 2.4% Girls (68%) Boys (34%)
- Maximum increase in girls 15-18 years old
SSRIs & Suicides—all ages 1991-2000
In Australia—Hall et al

- No overall change in suicides (< aged, >young)
- Steep increase in use of anti-depressants
- Inverse relation between anti-depressants & suicides
- ? Increased awareness of depression—better care
- ? Other psycho-social factors influence
- ?? Anti-depressants reduce depression
Dosing in managing agitation

6-10 years
- 1st line: Lorazepam 1-2 milligrams O/IMI
- 2nd line: Midazolam 5-20 milligrams intranasal/IMI

11-18 years (lower doses for the younger children)
- 1st line: Lorazepam
- 2nd Line: Midazolam 10-20 milligrams
- 3rd Line: Olanzapine 5-20 milligrams Wafer/IMI
- 4th Line: Haloperidol 2.5-10 milligrams IMI
Explanations for DSH

- Biased populations
- Non compliance or withdrawal effects
- Activation effect
- Manic switch
- ? Neurobiological differences in DSH & Suicide.
- Efficacy is not dose dependent but side effects are
Dosing of anti-depressants

- Fluoxetine: 10 - 60 milligrams
- Sertraline: 12.5 to 150 milligrams
- Fluvoxamine: 25 to 100 milligrams
- Citalopram & Escitalopram: 10-20 milligrams
- Mirtazapine: 15-45 milligrams
- Try each dose for 3-4 weeks before increasing
ANTIPSYCHOTICS

THE FIRST & SECOND GENERATION
INTRODUCTION

- 1950: Chlorpromazine
- Neuroleptic & antipsychotic
- SGA: Lower EPS risk & treats negative sx
- But ?higher cardiac & metabolic side effects
- Classified according to chemical structure, receptor binding & affinity, clinical profile.
- According to receptor binding-classified into typical & atypical.
- Then into typical high potency, moderate & typical low potency, atypical.
The childhood mental illnesses

- Early onset Schizophrenia (> 13 years)
- Very early onset Schizophrenia (< 13 years) (Werry)
- Rapid & Ultra rapid cyclers Bipolar mood disorder & mixed states
Results demonstrated that antipsychotic treatment with risperidone, olanzapine or aripiprazole led to significant improvements in symptomatology.

Treatment with a 10 mg daily dose of aripiprazole was associated with the lowest incidence of extrapyramidal symptoms and showed no significant weight gain.

If a treatment with antipsychotic drugs associated with significant weight gain as olanzapine or risperidone is needed, compensative measures should be soon considered.
## Earlier studies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Age range</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>200-800 mgs</td>
<td>12-16 yrs</td>
<td>McConville 2000</td>
</tr>
<tr>
<td>Clozapine</td>
<td>200-300 mgs</td>
<td>9-13 yrs</td>
<td>Turetz 1997</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5-20 mgs</td>
<td>9.4 yrs &gt;</td>
<td>Sholevar 2000</td>
</tr>
<tr>
<td>Risperidone</td>
<td>6.6 mgs</td>
<td>11-18 yrs</td>
<td>Armenteros 1997</td>
</tr>
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</table>
Eighteen studies were considered, all of which were unfortunately impaired by methodologic limitations, such as the paucity of long-term data and lack of a three-arm comparison (SGA vs SGA vs placebo).

The results of this review allow us to suggest the effectiveness of three SGAs (aripiprazole, olanzapine, and risperidone) in the short-term treatment of both early-onset schizophrenia and bipolar mania.
32 studies analyzing efficacy and/or tolerability of SGAs in children and adolescents with bipolar, autistic or disruptive behavior disorders, and Tourette syndrome were identified. SGAs efficacy on mania, extreme mood variability, irritability, aggression and disruptive behavior appears to be greater than for psychotic symptoms in schizophrenia.

In randomized studies, adverse effects were usually relatively minor, easily predictable and manageable, whereas long-term open-label studies have indicated that some adverse event, such as the metabolic effects, may be severe and potentially life threatening on the long-term.
This 24-week, three-site, controlled clinical trial randomized 124 children (4 through 13 years of age) with PDDs and serious behavioral problems to medication alone (MED; n = 49; risperidone 0.5 to 3.5 mg/day; if ineffective, switch to aripiprazole was permitted) or a combination of medication plus parent training (PT) (COMB; n = 75).

Both groups showed improvement but combo showed greater improvement in social & adaptive behaviours which reduced maladaptive behaviours.
The atypical antipsychotics (olanzapine, ziprasidone, quetiapine, aripiprazole) have shown some efficacy in improving certain behavioral symptoms of autistic disorder—primarily aggressiveness, hyperactivity, and self-injurious behavior.

- Evidence strongest for Olanzapine based on open label studies
- Aripiprazole has demonstrated efficacy in limited case series, with minimal adverse effects reported.
<table>
<thead>
<tr>
<th>SGA management of aggressive behaviour</th>
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</thead>
<tbody>
<tr>
<td>- Findling et al, Pandina et al 2006</td>
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<tr>
<td>- Reyes et al placebo controlled trial 2006</td>
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<tr>
<td>- Pappadopulos 2008</td>
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<tr>
<td>- Farmer  TOSCA (Treatment Of Child Aggression) Nov 2011</td>
</tr>
</tbody>
</table>
Metabolic adverse effects of SGA APs

- In recently issued guidelines, thresholds for antipsychotic-induced weight gain in adults have been set at a 5% increase or one point increase in BMI unit.
- No definition has reached a consensus in childhood and adolescence.
- More than 5% increase in weight within a three-month period; more than half a point increase in BMI Z score; between 85th and 95th BMI percentile plus one adverse health consequence (i.e. hyperglycaemia, dyslipidemia, hyperinsulinemia, hypertension, or orthopaedic, gallbladder, or sleep disorder); or more than 95th BMI percentile or abdominal obesity (i.e. abdominal circumference above 90th percentile).
Across 34 published head-to-head and placebo-controlled studies in youth with psychotic and bipolar disorders, weight gain ranged from 3.8 to 16.2 kg with olanzapine (n=353), 0.9-9.5 kg with clozapine (n=97), 1.9-7.2 kg with risperidone (n=571), 2.3-6.1 kg with quetiapine (n=133), and 0-4.4 kg with aripiprazole (n=451).

Data in autism and disruptive behavior disorders, available only for some antipsychotics, suggest greater weight gain, possibly due to less prior antipsychotic exposure.

Poly pharmacy increases risk
Dosing in psychosis

- Olanzapine: 2.5 to 25 milligrams
- Risperidone: 0.5 to 8 milligrams
- Quetiapine: 100 to 800 milligrams
- Aripiprazole 10-30 milligrams
- Clozapine: 150-300 milligrams
Conclusions

Psychosis & Bipolar mood disorder
- SGA Antipsychotics are effective in symptom relief & have fewer extrapyramidal adverse effects but have metabolic & cardiovascular effects

Autism, Intellectual disability, behavioral disorders
- Less clear evidence so a risk vs benefit decision has to be made. More studies required
Metabolic monitoring

- Known history or family history of diabetes &/or obesity &/or hyperlipidemia-do baseline bloods, repeat every 6 months if normal at baseline or more frequently if abnormal
- No known history-do bloods if weight gain occurs and goes beyond 5 kilos. Repeat if abnormal.
- If bloods remain abnormal after 3 tests and weight gain not managed with conservative measures but good psychosis control-consider endo consult and Metformin OR change to another AP
Metabolic monitoring

- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3143700/
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3950759/