Disclosure

Principal/Sub-Investigator, Consultant or Lecturer for the following companies:

- Bayer
- Bristol Myers Squibb
- Eli Lilly
- Johnson&Johnson
- Pfizer
- Plethora
- Polpharma
- Servier
- Verco

Conflict of interests according to this lecture: none
Questions

Sexual dysfunction in patients treated with antipsychotics

• How serious is the problem?
  • Frequency of SD due to AP-treatment
  • Compliance issues

• How APs influence sexual response?

• How to preserve sexual health when AP-treatment is needed?
  • EBM vs clinical reality
  • Management of post-AP SD
SD in schizophrenia patients – consider different causes

- Prevalence of SD 60% - 90%
  (Kodesh et al., 2003; Liu-Seifert et al., 2009; Macdonald et al., 2003)
- Effect of the disease?
  - Neurophysiological changes / common pathophysiology
  - Negative symptoms
  - Depressive symptoms
  - Social stigma
- Influence of co-existing medical conditions?
  - CVD, metabolic syndrome
  - Illicit alcohol/drug abuse
  - hiperprolactinemia
- Medication side-effects?
- Paucity of RCT’s!
Frequency of sexual dysfunction – comparison between APs

Montejo et al., J Sex Med 2010; 7: 3404-3413
Frequency of sexual dysfunction – comparison between APs

- Low rates of SD for quetiapine, ziprasidone, perphenazine and aripiprazole (16–27 %) vs high rates for olanzapine, risperidone, haloperidol, clozapine and thioridazine (40–60 %) [Meta-analysis by Serretti et al., Int Clin Psychopharmacol 2011]

- Low rates of SD in pts treated with quetiapine (18 %) compared to olanzapine (35 %), haloperidol (38 %) and risperidone (43 %) [Observational study by Bobes et al., 2003, n=636]

- No statistically significant differences in prevalence of SD in pts treated with haloperidol (71 %), risperidone (68 %), quetiapine (60 %) and olanzapine (56 %) [Observational study (IC-SOHO), n=3838; Dossenbach et al., Eur Psychiatry 2006]
The probability of post-APs sexual dysfunction is dose-dependent.
Compliance issues

- AP-related SD is one of the most important predictors of treatment compliance
  (Kelly & Conley, 2006; Perkins, 2002; Lambert i wsp., 2004; Byerly i wsp., 2007)
- Schizophrenia patients often indicate diminished desire and sexual experience but 62% report being sexually active (80% with stable course of the disease)
  (Thomson et al., 1997; Fuller & Torrey, 2001)
- Treatment-related SD are rarely reported spontaneously (Dervaux, 2005)
- Psychiatrists frequently do not address sexual health issues of their patients (Higgins et al., 2005; Murthy & Wylie, 2007; Peuskens, 1998)
Impact of APs on sexual functioning & treatment outcomes

- Impact of APs on central regulation of sexual response
- HSDD, FSAD and ED due to medication-related hyperprolactinemia
- 2nd generation (atypical) APs
  - Different influence on PRL level
  - Beneficial effect on negative symptoms
  - Common metabolic complications
APs’ clinical and side-effects profiles depend on their affinity to particular CNS receptors
Dopaminergic antagonism & sexual side effects

- inhibition of motivation/reward → decreased desire
- tubero-infundibular pathway - hiperprolactinemia
- Nigrostratial pathway – EPS, tardive dyskinesia, acatisia
- ↓nNOS expression and ↑DRD2 expression in MPOA and PVN
- DRD2-141C Ins/Del polymorphism – increased risk of post-AP SD
- DRD2 141C Del – protective factor (lower PRL)

La Torre et al., 2013; Zhang et al., 2011, 2012
Other pathways of post-AP sexual side effects

- Serotonergic receptor antagonism – delayed ejaculation
- Histamine receptor antagonism – sedation → impaired arousal
- Anticholinergic effect – reduced peripheral vasodilatation → ED
- Alpha-1 receptor blockade – reduced peripheral vasodilatation → priapism, decreased erection/lubrication, ejaculation abnormalities
- Calcium channels blockade
- Weight gain → metabolic complications

La Torre et al., 2013; Zhang et al., 2011, 2012
Hyperprolactinemia due to antipsychotic treatment

Table 1. First and Second Generation Antipsychotics and their propensity to cause hyperprolactinaemia

<table>
<thead>
<tr>
<th></th>
<th>Sustained hyperprolactinaemia</th>
<th>Transient hyperprolactinaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Perphenazine</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Thioridazine</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Second Generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amisulpride</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td></td>
<td>✅</td>
</tr>
<tr>
<td>Clozapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
<td>✅</td>
</tr>
<tr>
<td>Risperidone</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Sertindole</td>
<td></td>
<td>✅</td>
</tr>
<tr>
<td>Zoepine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Holt & Pevelert, 2011
The impact of post-AP hyperprolactinemia on the incidence of SD remains unclear

- Decreased sexual desire
- ED / impaired lubrication
- Orgasmic / ejaculatory dysfunction
- Testosterone / estradiol decrease
- Disturbed menstruation

(Liu-Seifert et al., 2009; Fortier et al., 2003)

Johnsen et al., 2011
A Pilot Study to Determine a Prolactin Threshold that Identifies Improved Sexual Functioning when Switching from a Prolactin-Elevating to a Prolactin-Neutral Antipsychotic

Matthew J. Byerly 1, Paul A. Nakonezny
Clinical Schizophrenia & Related Psychoses (2010)

<table>
<thead>
<tr>
<th>Prolactin Cutpoint (ng/mL)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Odds Ratio</th>
<th>$\chi^2$</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>100</td>
<td>16.7</td>
<td>44.4</td>
<td>100</td>
<td>1.0</td>
<td>0.001</td>
<td>0.97</td>
</tr>
<tr>
<td>8</td>
<td>87.5</td>
<td>33.3</td>
<td>46.7</td>
<td>80.0</td>
<td>3.5</td>
<td>1.03</td>
<td>0.31</td>
</tr>
<tr>
<td>11</td>
<td>75.0</td>
<td>41.7</td>
<td>46.2</td>
<td>71.4</td>
<td>2.14</td>
<td>0.57</td>
<td>0.45</td>
</tr>
<tr>
<td>14</td>
<td>75.0</td>
<td>50.0</td>
<td>50.0</td>
<td>75.0</td>
<td>3.00</td>
<td>1.21</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>17</strong></td>
<td><strong>75.0</strong></td>
<td><strong>75.0</strong></td>
<td><strong>66.7</strong></td>
<td><strong>81.8</strong></td>
<td><strong>9.00</strong></td>
<td><strong>4.34</strong></td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>22</td>
<td>62.5</td>
<td>75.0</td>
<td>62.5</td>
<td>75.0</td>
<td>5.00</td>
<td>2.65</td>
<td>0.10</td>
</tr>
<tr>
<td>24</td>
<td>50.0</td>
<td>75.0</td>
<td>57.1</td>
<td>69.2</td>
<td>3.00</td>
<td>1.28</td>
<td>0.26</td>
</tr>
<tr>
<td>25</td>
<td>50.0</td>
<td>83.3</td>
<td>66.7</td>
<td>71.4</td>
<td>5.00</td>
<td>2.35</td>
<td>0.12</td>
</tr>
<tr>
<td>34</td>
<td>37.5</td>
<td>83.3</td>
<td>60.0</td>
<td>66.7</td>
<td>3.00</td>
<td>1.06</td>
<td>0.30</td>
</tr>
<tr>
<td>48</td>
<td>25.0</td>
<td>83.3</td>
<td>50.0</td>
<td>62.5</td>
<td>1.67</td>
<td>0.21</td>
<td>0.65</td>
</tr>
<tr>
<td>52</td>
<td>25.0</td>
<td>91.7</td>
<td>66.7</td>
<td>64.7</td>
<td>3.67</td>
<td>0.96</td>
<td>0.33</td>
</tr>
<tr>
<td>61</td>
<td>0.0</td>
<td>91.7</td>
<td>0.0</td>
<td>57.9</td>
<td></td>
<td>0.001</td>
<td>0.98</td>
</tr>
</tbody>
</table>
STAR Study
(Schizophrenia Trial of Aripiprazole)

Figure 2
Mean change from baseline in ASEX Total score at week 26 by drug (OC).

Figure 4
Mean change from baseline in serum prolactin concentration at week 26 by drug (OC).

Hanssens et al.; BMC Psychiatry 2008, 8:95
Priapism

- possible side effect of all APs
- particularly for phenothiazines
  - chlorpromazine, fluphenazine and thioridazine (Compton & Miller, 2001)
- Case reports of priapism
  - aripiprazole (Mago et al., 2006)
  - clozapine and flupenthixol (Orazzo et al., 2013)
  - olanzapine, quetiapine, risperidone (Cutler, 2003; Penaskovic et al., 2010; Torun et al., 2011)
  - ziprasidone (Kaufman et al., 2006; Reeves & Kimble, 2003)
Medication choice in the treatment of psychosis

- Efficacy vs tolerability
- Compliance issues
- Acute treatment vs relapse prevention
**Table:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment</th>
<th>Efficacy (SMD with 95% CI)</th>
<th>All cause discontinuation (OR with 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLO</td>
<td>0.16 (0.09 to 0.23)</td>
<td>0.01 (0.00 to 0.03)</td>
<td>0.01 (0.00 to 0.03)</td>
</tr>
<tr>
<td>AMI</td>
<td>0.12 (0.04 to 0.20)</td>
<td>0.01 (0.00 to 0.03)</td>
<td>0.01 (0.00 to 0.03)</td>
</tr>
<tr>
<td>OLA</td>
<td>0.06 (0.03 to 0.09)</td>
<td>0.01 (0.00 to 0.03)</td>
<td>0.01 (0.00 to 0.03)</td>
</tr>
<tr>
<td>PAL</td>
<td>0.04 (0.02 to 0.06)</td>
<td>0.01 (0.00 to 0.03)</td>
<td>0.01 (0.00 to 0.03)</td>
</tr>
<tr>
<td>ZOT</td>
<td>0.03 (0.01 to 0.05)</td>
<td>0.01 (0.00 to 0.03)</td>
<td>0.01 (0.00 to 0.03)</td>
</tr>
</tbody>
</table>

**Figure:** Efficacy and all-cause discontinuation of antipsychotic drugs

Leucht et al., Lancet 2013; 382: 951 - 962
Management of SD due to AP-treatment

- Dose reduction
- Drug holiday (risk of relapse)
- Switching to another drug
- Adjunctive medication

Low level of evidence!

- Paucity of RCTs
- Small samples, short studies
## RCTs for the treatment of AP-induced SD/hiperPRL

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Scale used</th>
<th>Prolactin levels</th>
<th>Induced by</th>
<th>Study design</th>
<th>Duration (weeks)</th>
<th>N</th>
<th>Mean age (years)</th>
<th>Diagnosis</th>
<th>Intervention</th>
<th>Participants who completed the study</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byerly et al. (2006)</td>
<td>ASEX scale (sexual drive, arousal, penis erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm)</td>
<td>Risperidone</td>
<td>Randomized double-blind, pilot trial</td>
<td>6</td>
<td>42 (22 men, 20 women)</td>
<td>42.3</td>
<td>Schizophrenia or schizoaffective disorder*</td>
<td>1. Switch to quetiapine, mean dose 200 mg/day 2. Risperidone continuation, 4.1 mg/day</td>
<td>100%</td>
<td>Sexual functioning measured by ASEX scale did not differ significantly between quetiapine switch versus risperidone continuation</td>
<td></td>
</tr>
<tr>
<td>Nakonezny et al. (2007)</td>
<td>ASEX scale (sexual drive, arousal, penis erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm)</td>
<td>Risperidone</td>
<td>Randomized double-blind, pilot trial</td>
<td>6</td>
<td>22 men</td>
<td>40.8</td>
<td>Schizophrenia or schizoaffective disorder*</td>
<td>1. Switch to quetiapine, mean dose 200 mg/day 2. Risperidone continuation, 4.1 mg/day</td>
<td>100%</td>
<td>Higher serum prolactin level was related to greater impairment of sexual functioning in male outpatients who were treated with risperidone but not with quetiapine</td>
<td></td>
</tr>
<tr>
<td>Shim et al. (2007)</td>
<td>Prolactin-Related Adverse Event Questionnaire (menstrual disturbances and galactorrhea)</td>
<td>Haloperidol</td>
<td>Randomized, double-blind, placebo controlled trial at Inje University</td>
<td>8</td>
<td>54 (22 men, 32 women)</td>
<td>39.5</td>
<td>Schizophrenia*</td>
<td>1. Adjunctive aripiprazole, 15-30 mg/day 2. Placebo as adjunctive treatment</td>
<td>96.2%</td>
<td>Adjuvative aripiprazole led to prolactin level normalization in 84.6% of patients, resulting in reinstatement of menstruation in women</td>
<td></td>
</tr>
<tr>
<td>Gopalakrishnan et al. (2006)</td>
<td>International Index of Erectile Function (erection dysfunction)</td>
<td>Haloperidol, olanzapine, clozapine, fluphenazine decanoate</td>
<td>Randomized, double-blind, placebo controlled trial</td>
<td>2</td>
<td>52 men</td>
<td>35.1</td>
<td>Schizophrenia or delusional disorder*</td>
<td>1. Adjunctive sildenafil, 25-50 mg 2. Placebo</td>
<td>96.9%</td>
<td>Improvement in number and mean duration of erections and in combined number of satisfactory times of intercourse</td>
<td></td>
</tr>
<tr>
<td>Kodesh et al. (2003)</td>
<td>Sexual Functioning Scale (sexual drive, arousal, penis erection/vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm)</td>
<td>Perphenazine or haloperidol</td>
<td>Randomized double-blind, placebo-controlled, crossover study</td>
<td>3</td>
<td>10 men</td>
<td>44.8</td>
<td>Schizophrenia*</td>
<td>1. Selegiline, 15 mg/day as adjunctive treatment 2. Placebo</td>
<td>100%</td>
<td>It was not found to be effective in improving any domain of sexual functioning, despite a significant decrease in prolactin levels</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (1995)</td>
<td>Prolactin levels</td>
<td>Haloperidol</td>
<td>Double-blind placebo controlled trial</td>
<td>6</td>
<td>40 (20 men, 20 women)</td>
<td>34</td>
<td>Schizophrenia*</td>
<td>1. Cyproheptadine, 24 mg/day 2. Placebo</td>
<td>87%</td>
<td>Cyproheptadine augmentation did not reduce the plasma prolactin level but did induce a decrease in the plasma cortisol level</td>
<td></td>
</tr>
</tbody>
</table>

Nunes et al. Journal of Sex & Marital Therapy 2012; 38(3): 281-301
open-label / noncontrolled studies

• Improved SF after switching to aripiprazole, quetiapine, olanzapine, ziprasidone
• Improved SF domains after adding sildenafil, vardenafil, amantadine (+PRL decrease, no improvement in ejaculation), bromocriptine
• PRL decrease after adding cabergoline

Nunes et al. Journal of Sex & Marital Therapy 2012; 38(3): 281-301
Schmidt et al., The Cochrane Library 2012, 11: 1-66
Menagement of SD due to AP-treatment

- Consider dose reduction

  - No
    - Consider switch to AP with less impact on SF
      - Improve SF
        - Continue treatment
      - Persisting SD
        - Change to another AP, combination therapy or use adjunctive medication (i.e. PDE5-I)
      - No possibility for change to different AP
        - Use adjunctive medication to (i.e. PDE5-I)
        - Consider changing AP in the future
  - Yes
    - Observation, repeat assessment of SF
      - Improvement of SF
        - Continue treatment
      - Persisting SD
Take home messages

- Side-effects of AP treatment may seriously impact patients’ sexual function and their compliance
- Need for direct questioning about drug-induced SD
- Decision-making process determined by symptom profile, drug effectiveness and tolerability (including SF)
  - If possible, avoid PRL-raising APs
  - If possible, use „sex-friendly” APs:
    - Aripiprazole, Quetiapine (RCTs, evidence 1b)
    - Olanzapine, Ziprasidone (evidence, 2b)
    - Perphenazine? Clozapine?
- Use remedies like PDE-5 inhibitors (evidence 1b)
- Prophylaxy of metabolic complications of 2nd generation APs
- Remember about other symptoms affecting sexual response and relationship factors
- Need for further research to assess potential superiority of certain APs!