Description of included studies

Table 1: Studies on effects of pharmacological interventions in forensic psychiatry

Title Author Country Reference	Context/ setting	Type of study	Population	Intervention	Control	Outcome	Results	Risk of bias assessed by SBU Comment
Does clozapine promote employability and reduce offending among mentally disordered offenders? Balbuena et al. Origin: Canada Ref number: [19]	Forensic psychiatric hospital, dedicated to high-risk, high-need, federally sentenced (2 years or more) mentally disordered offenders	Non-randomized retrospective study	Clozapine group: n=65, mean age 34 (63 male, 2 female). Control group: N=33, mean age 37 (31 male, 2 female) All patients and controls had psychosis or related	Clozapine treatment for 6 months Dose or administration form is not given	Treatment with traditional antipsychotics at the same hospital for 6 months	Frequency of noncompliant incidence, change in BPRS total score Institutional pay was recorded as a measure of good behavior, presumably reflecting life quality.	Clozapine-group: Mean pay increase: 38 of 65 patients got increased pay level Mean BPRS score: 38.5 Mean number of posttreatment offences during 12 months: 0.62 Control group: Mean pay increase: 10 of 33 controls got	High risk **Comment**: Risk of selection bias. The effect of clozapine may be under-estimated because of a negative selection (all patients in the clozapine group were non-responders to traditional antipsychotics). Lack of compliance analysis in the clozapine group in contrast to the control group. Frequency of

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			disorders according to DSM-IV. No information on co-morbidity.				increased pay level Mean BPRS score: 30.4 Mean number of posttreatment offences during 12 months: 1.37	aggressiveness (not levels) was recorded. Number of interactions were not recorded during the 6 months treatment period, but during the six-month period after. Unclear whether patients during the latter six-month period were on clozapine or other antipsychotics.
Risperidone in the management of violent, treatment-resistant schizophrenics hospitalized in a maximum security forensic facility. Beck et al. Origin: US Ref number: [24]	Three forensic treatment wards at state mental hospital	Non-randomized retrospective study	Risperidone group: n=10, mean age 39 (all male) Controls: n=10, mean age 40 (all male) All patients and controls had schizo-phrenia or schizoaffective disorders according to DSM-IV. No	Risperidone treatment for 6+6 months, 6 mg/day, administration form not given	Treatment with traditional antipsychotics (equivalent with 2,000 units of chlor-promazine) at the same hospital for 6+6 months	Scores on TSBC, reflecting clinical functioning Frequency counts of aggressive behaviour and bizarre motor behaviours were recorded.	No difference between risperidone patients and controls with regards to overall clinical functioning or aggressive behaviour	High risk **Comment**: Lack of information in the control group. The frequency of aggressive behaviour was recorded only. In the control group only chlorpromazine equivalents were given instead of a detailed description of what antipsychotics used.

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			information on co-morbidity.					
Lithium carbonate in chronic schizophrenia – a brief trial of lithium carbonate added to neuroleptics for treatment of resistant schizophrenic patients. Collins, Larki, Shubsachs. Origin: UK Ref number: [25]	High security hospital	Randomized single-blind trial	Lithium add-on: n=21, mean age 39 (all male) Controls: n=22, mean age 38 (all male) All patients and controls had schizophrenia or related disorders according to DSM-III. No information on co-morbidity.	Addition of lithium carbonate to traditional antipsychotics 400 mg twice daily	Treatment with various antipsychotics throughout the treatment period	Psychiatric conditions according to the Manchester Scale (modified to separate flattening and incongruity of affect) and SANS Scale	Lithium add-on showed no improvement in psychiatric condition	High risk **Comment:** High drop-out in the treatment group. Individual antipsychotic treatment was not reported. For diagnosis DSM III was used.
Clozapine treatment of long-standing schizophrenia and serious violence: A two-year follow-	High security hospital	Non-randomized retrospective study	Clozapine group: n=50 (44 male, 6 female). Information on age not	Clozapine treatment baseline before, after 6 months,	No control group, effects were compared with baseline values	Frequency of violence and self-harm, discharge rate from the hospital	50% of patients showed a reduction in positive symptoms and aggressive	High risk **Comment:** No internationally accepted rating scales were used. Negative

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up study of the first 50 patients treated with clozapine in Rampton high security hospital. Dalal, Larkin, Leese, Taylor. Origin: UK Ref number: [20]			given, unless that mean age at first psychiatric contact was 20 years Control group: n=50 Schizophrenia or schizo-affective disorder. Local rating scales of positive symptoms were used.	after 1 year, after 2 years No specific doses of clozapine are given, only, in some cases, chlorpromazine-equivalent doses.	50 non-clozapine patients from the same hospital were used as controls, but for the comparison of discharge rate only.	Positive symptoms according to Health of the Nation Outcome Scales	behaviour after 2 years of treatment. Significant increase in discharge rate in patients that continued treatment compared to those that discontinued clozapine. However, this discharge rate was not higher compared to the controls.	symptoms were not recorded. Thus, unclear patient population. Missing information of the control group.
Effects of quetiapine and olanzapine in patients with psychosis and violent behavior: A pilot randomized, open-label, comparative study. Gobbi, Comai, Debonnel.	High security	Randomized study	Quetiapine group: n=8, mean age 43 (7 male, 1 female) Olanzapine group: n=7, mean age 38 (all male) Patients were diagnosed	Comparison between Quetiapine treatment (10 weeks, mean dose 475 mg/day) and Olanzapine treatment (10 weeks,	Comparison between quetiapine and olanzapine No control group, two different treatment groups.	Impulsive and aggressive behaviour according to "Modified Overt Aggression Scale" and "Impulsivity Rating Scale" Psychotic symptoms according to	Both drugs decreased impulsivity and psychotic symptoms. No significant difference between the drugs were observed. Quetiapine, better than	High risk **Comment**: Sponsored study. Vague information on medication at baseline (day 0 prior to treatment).

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Origin: Canada Ref number: [26]			with schizo-phrenia, schizoaffective disorder, or paranoid disorder (DSM-IV).	mean dose 15 mg/day)		BPRS, PANSS, and CGI	olanzapine improved symptoms of depression.	
Efficacy of topiramate, valproate, and their combination on aggression/agitation behavior in patients with psychosis. Gobbi, Gaudreau, Leblanc. Origin: Canada Ref number: [27]	High security	Non-randomized retrospective study	Topiramate group: n=16, mean age 37 (34 male, 3 female) Valproate group: n=16, mean age 39 (all male) Combination group: n=13, mean age 41 (12 male, 1 female) Patients were diagnosed with schizophrenia, schizoaffective disorder, any subtype of delusional	Add-on treatment (8-12 weeks) to traditional antipsychotics with topiramate (mean dose 250 mg/day), valproate (dose corre-sponding to plasma con-centration of 700 µM), or a combination of both drug	Three different treatment groups	Aggression (Overt Aggression Scale), agitation (Agitation-Calmness Evaluation Scale), psychotic episodes (BPRS), number of therapeutic isolation and surveillance interventions	All groups showed a reduction in agitation, aggressive behaviour. Valproate group and the combination of topiramate and valproate showed a reduction in psychotic episodes.	High risk **Comment**: Only part of the data was analysed in a blind manner. A selection of patients was made - only patients being able to tolerate topiramate/valproate were chosen. Greater loss of patients in topiramat-group.

Title Author Country Reference	Context/ setting	Type of study	Population	Intervention	Control	Outcome	Results	Risk of bias assessed by SBU Comment
			disorder, or bipolar disorder.					
Clozapine's Effect on Recidivism Among Offenders with Mental Disorders. Mela, Depiang. Origin: Canada Ref number: [21]	Open care patients from Regional Psychiatric Centre	Non-randomized retrospective study	Clozapine treatment: n= 41 Non-clozapine: n=21 Age or gender not given Offenders with mental disorders	Clozapine treatment more than 6 weeks in open care, dose titrated to therapeutic relevance. 2-years follow up	Treatment with antipsychotics other than clozapine	Number of reoffending behaviour (nonviolent, violent and sexual), time from release to the first offense and crime-free time	The clozapine group had a lower, although non-significant, incidence of all of the categories of reoffending, except sexual. Time from release to first offense longer in the clozapine group. Crime-free time longer in the clozapine group.	High risk **Comment:** Compliance not accounted for during the 2 years of follow-up. Contact with the health professionals may vary between the groups. Diagnosis not specified. In the comparison group various antipsychotics were used. The effect of clozapine may be underestimated because of a negative selection (all patients in the clozapine group were non-responders to traditional antipsychotics).
Impact of clozapine versus haloperidol on conditional	Psychiatric Rehabilitation Centre	Non-randomized retrospective study	Haloperidol treatment: n=78	Clozapine treatment	Two treatment groups: comparison	Psychiatric symptoms according to GAF	Haloperidol group: 59% showed improved GAF scores. 33%	High risk **Comment**: Various diagnosis, including

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release time and rates of revocation in a forensic psychiatric population. Stoner, Wehner Lea, Dubisar, Roebuck-Colgan, Vlach. Origin: US Ref number: [22]	patients hospitalized due to forensic court commitment, security level unclear.		Clozapine treatment n=21 Total sample: 69 male and 15 women Patients were diagnosed with schizo-phrenia or substance abuse.	Haloperidol treatment (either orally, mean dose 15.5 mg/day, or intra-muscularly, mean dose 206 mg every 4th week)	between clozapine and haloperidol	Conditional release Revoked conditional release	successfully obtained conditional release. Clozapine group: 86% showed improved GAF scores. 38% successfully obtained conditional release. Periods of conditional release before revocation were longer in the clozapine group.	both schizophrenia and drug abuse - groups were not homogenous. Some patients were treated by a combination of haloperidol and clozapine. Haloperidol was given either orally every day or intramuscularly every 4 weeks. The effect of clozapine may be underestimated because of a negative selection (all patients in the clozapine group were non-responders to traditional antipsychotics).
Clozapine in special hospital: A retrospective case-control study. Swinton, Haddock. Origin: UK Ref number: [23]	High security hospital	Retrospective case-control study	Clozapine group: n= 106, mean age 29 (73 male, 33 female) Non-clozapine group: n= 106, mean age 30	Clozapine treatment	Treatment with antipsychotics other than clozapine at the same hospital for	Evaluation of discharge rates	Clozapine group achieved increased rates of discharge when compared with non- clozapine group. It took more than one year until this	High risk **Comment:** relatively high drop-out. Some female cases in the study may not have had a diagnosis of schizophrenia.

Title Author Country Reference	Context/ setting	Type of study	Population	Intervention	Control	Outcome	Results	Risk of bias assessed by SBU Comment
			(73 male, 33 female) Diagnosis: mainly schizophrenia.				effect was obtained	No information on the treatment of the non-clozapine group.
High-dose antipsychotic medication in maximum security. Tavernor, Swinton, Tavernor. Origin: UK Ref number: [28]	High security hospital	Retrospective case-control study	High-dose group: n=32, mean age 39 Control group: n=32, mean age 38 No information on gender. Diagnosis of schizophrenia (62) or schizoaffective disorder (2)	High doses of traditional antipsychotic drugs	Patients with standard doses of antipsychotic drugs	Psychiatric symptoms evaluated by BPRS, GAS, SDAS, and NOSIE	Cases had higher BPRS total score than controls, as well as neurological side-effects. Cases were rated as more aggressive than controls. Conclusion: little benefit for the use of high-dose antipsychotics.	High risk **Comment:** Selection bias where cases had worse psychiatric symptoms and may have been prescribed a high-dose antipsychotic drug. Many patients received a combination of antipsychotic drugs and doses of antipsychotics were only given in equivalents of chlorpromazine. The antipsychotic drugs used are not specified. It is unclear whether each case received the same antipsychotic drug as the matched control.

Table 2: Systematic reviews on chosen comorbidities

First author Year Reference	Objectives Population	Intervention Comparison Outcome	Number of included studies (participants) Year -search executed	Main results and the estimated level of evidence according to authors	Risk of bias assessed by SBU
Psychotic disorder + co-morbid substance use					
Wilson 2016 (cannabis) Ref. number: [31]	To perform a systematic review of antipsychotic treatment in adults with a psychotic disorder and a co-morbid cannabis use	Pharmacological intervention with different antipsychotics Psychotic symptoms and degree of cannabis use as outcome measures	22 studies, 13 experimental and 9 observational including a total of 1 543 participants Search executed in 2014	Olanzapine, risperidone, haloperidol, clozapine and ziprasidone reduced psychotic symptoms Several antipsychotics did also reduce measures of cannabis use There were preliminary evidence supporting that clozapine may be superior to other antipsychotics in reducing psychotic symptoms and measures of cannabis use	Moderate
Sawicka 2017 (alcohol) Ref. number: [30]	To perform a systematic review of naltrexone treatment in adults with a psychotic disorder and a co-morbid alcohol use disorder	Pharmacological intervention with the opioid antagonist naltrexone Different measures of alcohol consumption and psychopathology as outcome measures	9 studies, 4 of them were randomized control trials A total of 798 participants were included, 273 out of them had a psychotic disorder Search executed in 2016	Naltrexone reduced measures of alcohol consumption as compared to placebo The effect of naltrexone was similar to the effect of disulfiram and modestly superior to acamprosate No evidence was available regarding the effect of naltrexone on measures of psychopathology	Moderate

First author Year Reference	Objectives Population	Intervention Comparison Outcome	Number of included studies (participants) Year -search executed	Main results and the estimated level of evidence according to authors	Risk of bias assessed by SBU
McLoughlin 2014 (cannabis) Ref. number: [29]	A Cochrane Database systematic review and meta-analyses of randomised controlled trials with treatment of cannabis use in adults with a psychotic disorder	Pharmacological intervention with different antipsychotics	8 studies including a total of 530 participants Search executed in 2013	Olanzapine, risperidone and clozapine reduced measures of cannabis use Results were limited and inconclusive	Low
Arranz 2017 (substance use) Ref. number: [32]	To perform a systematic review on the efficacy of clozapine on substance use disorders in persons with schizophrenia	Pharmacological intervention with clozapine Degree of abuse of different substances as outcome measures	14 studies, 5 nicotine use (727 participants) and 9 other than nicotine (999 participants) Search executed in 2017	Clozapine reduced measures of nicotine use, however, the degree of evidence was low Clozapine was superior to traditional antipsychotics in reducing measures of poly-substance use, especially cannabis use	Moderate
Sabioni 2013 (cocaine) Ref. number: [33]	To perform a systematic review of pharmacological treatment in adults with a psychotic disorder and a co-morbid cocaine dependence	Pharmacological intervention with typical and atypical antipsychotics and a monoamine transporter antagonist Outcome measures were different measures of cocaine use	7 studies with a total of 148 participants Search executed in 2012	Aripiprazole, and possibly risperidone and olanzapine, reduced measures of cocaine use Results were limited and inconclusive due to methodological heterogeneity and lack of placebo-controlled studies	Moderate
Psychotic disorder + aggressive behaviour					

First author Year Reference	Objectives Population	Intervention Comparison Outcome	Number of included studies (participants) Year -search executed	Main results and the estimated level of evidence according to authors	Risk of bias assessed by SBU
Khushu 2016 Ref. number: [34]	A Cochrane Database systematic review of randomised controlled trials with haloperidol treatment of long-term aggression in adults with a psychotic disorder	Pharmacological treatment with haloperidol Outcome measures were different measures of aggression	1 study with a total of 110 participants Search executed in 2015	No evidence for a decrease in aggression Comparisons between haloperidol versus clozapine and olanzapine were inconclusive due to skewed data	Low
Psychotic disorder + personality disorder					
No systematic reviews	-	-	-	-	-
Psychotic disorder + ADHD					
No systematic reviews	-	-	-	-	-
Psychotic disorder + intellectual disability					
Ayub 2015 (Clozapin) Ref. number: [35]	A Cochrane Database systematic review of randomised controlled trials determining the effects of clozapine for treating adults with a dual diagnosis of	Pharmacological treatment with clozapine	No study fulfilled the inclusion criterion of being a randomised controlled trial	No results	Low

First author Year Reference	Objectives Population	Intervention Comparison Outcome	Number of included studies (participants) Year -search executed	Main results and the estimated level of evidence according to authors	Risk of bias assessed by SBU
	psychosis and intellectual disability		Search executed in 2015		
Psychotic disorder + Autism					
No systematic reviews	-	-	-	-	-
Autism + co-morbid substance use					
No systematic reviews	-	-	-	-	-
Autism + aggressive behaviour					
No systematic reviews	-	-	-	-	-
Autism + personality disorder					

First author Year Reference	Objectives Population	Intervention Comparison Outcome	Number of included studies (participants) Year -search executed	Main results and the estimated level of evidence according to authors	Risk of bias assessed by SBU
No systematic reviews	-	-	-	-	-
Autism + ADHD + aggressive behaviour					
No systematic reviews	-	-	-	-	-
Autism + intellectual disability					
No systematic reviews	-	-	-	-	-
Personality disorder + co-morbid substance use					
No systematic reviews	-	-	-	-	-
Personality disorder + aggressive behaviour					

First author Year Reference	Objectives Population	Intervention Comparison Outcome	Number of included studies (participants) Year -search executed	Main results and the estimated level of evidence according to authors	Risk of bias assessed by SBU
Huband 2010 **Ref. number: [36]**	A Cochrane Database systematic review and meta-analyses of prospective placebo-controlled trials of antiepileptic agents taken by adults with recurrent aggression	Pharmacological treatment with antiepileptic agents Outcome measures were frequency and intensity of aggressive outbursts	14 studies with o total of 672 participants Search executed in 2009	Sodium valproate, carbamazepine, oxcarbazepine and phenytoin reduced aggressive behaviour, but displayed differential effects in different patient groups (borderline personality disorder, conduct disorder and pervasive developmental disorder) The evidence was insufficient to allow firm conclusions	Low
Ingenhoven 2010 **Ref. number: [37]**	To perform a systematic review and meta-analyses of randomised controlled trials with pharmacological treatment of different symptom domains for borderline and schizotypal personality disorder	Pharmacological interventions with antipsychotics, antidepressants and mood stabilizers Outcome measures were various symptom domains for personality disorder such as anger, impulsive-behavioural dyscontrol and global functioning	21 studies with a total of 733 participants Search executed in 2008	The three groups of agents reduced symptoms in different ways Antipsychotics had a moderate to large effect on anger but no effect on impulsive-behavioural dyscontrol Antidepressants had a small effect on anger but no effect on impulsive-behavioural dyscontrol Mood stabilizers had a very large effect on impulsive-behavioural dyscontrol and anger, and a more pronounced positive effect on global functioning	Moderate
Ingenhoven 2011 **Ref. number: [38]**	To perform a systematic review and meta-analyses of randomised controlled trials with antipsychotic treatment of	Pharmacological interventions with antipsychotics	11 studies with a total of 2 281 participants Search executed in 2011	Antipsychotics had a small positive effect on cognitive-perceptual symptoms, mood lability and global functioning, and a more pronounced effect on anger reduction	Moderate

First author Year Reference	Objectives Population	Intervention Comparison Outcome	Number of included studies (participants) Year -search executed	Main results and the estimated level of evidence according to authors	Risk of bias assessed by SBU
	different symptom domains for borderline personality disorder	Outcome measures were various symptom domains for personality disorder such as anger, impulsive-behavioural dyscontrol and global functioning		Antipsychotics did not have any effect on impulsive behavioural dyscontrol.	
Nosé **2006** **Ref. number: [39]**	To perform a systematic review and meta-analyses of pharmacological treatment of different symptom domains for borderline personality disorder	Pharmacological interventions with antipsychotics, antidepressants and mood stabilizers Outcome measures were various symptom domains for personality disorder such as affective instability, anger, impulsivity and aggression	20 studies with a total of 844 participants Search executed in 2006	Antipsychotics had a positive effect on impulsivity and aggression Antidepressants and mood stabilizers had positive effects on affective instability and anger but had no effects on impulsivity and aggression	Low
Stoffers **2010** **Ref. number: [40]**	A Cochrane Database systematic review and meta-analyses of randomised controlled trials of pharmacological interventions for borderline personality disorder	Pharmacological interventions with typical and atypical antipsychotics, antidepressants, mood stabilizers and	28 studies with a total of 1 742 participants Search executed in 2009	Total borderline personality severity was not affected by any drug Data from symptom domains suggested only marginal effects of typical antipsychotics and antidepressants, but supported the use	Low

First author Year Reference	Objectives Population	Intervention Comparison Outcome	Number of included studies (participants) Year -search executed	Main results and the estimated level of evidence according to authors	Risk of bias assessed by SBU
		dietary supplementation Outcome measures were total borderline personality disorder severity, distinct symptom domains for personality disorder, and psychopathology not associated to personality disorder		of atypical antipsychotics, mood stabilizers and omega-3-fatty acids Atypical antipsychotics and mood stabilizers had positive effects on the domains of interpersonal problems, impulsivity and anger	
Varghese 2010 Ref. number: [41]	To perform a systematic review and meta-analyses of randomised controlled trials of topiramate treatment for anger control	State anger, trait anger, anger in, anger out and anger control were outcome measures	5 studies with a total of 291 participants Search executed in 2009	Topiramate had positive effects on all outcome measures for hostility and aggression The included studies were small and the groups of participants were heterogeneous with regard to psychiatric diagnoses	Low
Personality disorder + ADHD + aggressive behaviour					
No systematic reviews	-	-	-	-	-
Personality disorder + intellectual disability					

First author Year Reference	Objectives Population	Intervention Comparison Outcome	Number of included studies (participants) Year -search executed	Main results and the estimated level of evidence according to authors	Risk of bias assessed by SBU
No systematic reviews	-	-	-	-	-

Table 3: Studies on experiences of pharmacological interventions in forensic psychiatry

Study Author Year Country Reference	Method	Population and setting	Study findings	Methodological limitations assessed by SBU
Prisoners' experiences of antipsychotic medication: influences on adherence Mills et al. 2011 UK Ref. number: [43]	30-minute semi-structured interview The interview schedule covered personal knowledge and awareness of illness and medication; past experiences of medication and adherence history; experiences and views of current medication and treatment; methods of medication avoidance and views of future treatment and likelihood of adherence after leaving prison. The data was analyzed using a content analysis method. The data were then coded according to the emerged themes, and the coded segments of data were organized using Tesch's (1990) method of "de contextualizing" and "re contextualizing", which helps to condense and expand data through new organizing principles.	Of the 44 participants in the study, 36 were males, and 8 were females. Their ages ranged between 19 and 61, with a mean age of 37. All but six were prescribed antipsychotic medication for the treatment of a psychotic disorder, with the remainder being prescribed this medication for personality disorder. Thirty-two participants had been a psychiatric inpatient. Sixty-four per cent were prescribed atypical antipsychotics. The fieldwork took place in three local prisons, two male category B (medium secure) prisons, and one female prison and involved prisoners both on remand and sentenced.	• Benefits of antipsychotic medication • Past non-adherence • Medication side effects • Relationships with clinicians	Moderate Unclear who performed the interviews, what relationship the researchers had to the participants and how they handled their preconceptions in relation to the data collection and analysis.