Results: In 2022, there were 91 deaths for the city and county (14.8/100,000) significantly higher than (8.14/100,000) in England and Wales (X^2=16.4, p<0.00001). The city had significantly more deaths (N=67;25.0/100,000, X^2=95.6, p<0.00001) versus the county (N=18;5.2/100,000). Mean age of death 43.2±9.0 and 23% were women. Most deaths in the county occurred in urban areas. Median age of death for Males was 42.6 yrs. and Females 45.2 yrs. (SD±9.0). Most implicated drug causing death was heroin and morphine (23.1%), methadone (16.5%) like national data, whilst benzodiazepines (15.4%) were higher than national (p>0.05). Most deaths were caused by more than one implicated drug 82.4%. 64.8% of deaths occurred in a person known to be using drugs. Many deaths had methadone implicated (N=28; 30.8%) and 50 deaths had methadone at PM of which 11 were prescribed. Most deaths (N=55; 64.7%) occurred in the top decile of IMD and occurred in the top 4.4% most deprived neighbourhoods.
Conclusion: Socioeconomic deprivation was associated with higher rates of drug-related deaths; most deaths occurred in the most deprived areas. Addressing deprivation-related risks in economically challenged areas is critical to effectively tackling drug deaths and health inequalities. The cause of death was most often opioids and strategies such as take-home naloxone and optimising opioid substitution treatment will be vital to reduce deaths. We note a high proportion of deaths had methadone, which was not prescribed, present at postmortem, indicating that prescribed methadone may have been diverted. Drug services may consider strategies to increase use of supervised consumption as per guidelines to reduce diversion and associated deaths.

A Spatial Covariance ^{123}5IA-85380 SPECT Study of α4β2 Nicotinic Receptors in Dementia with Lewy Bodies

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Aims: Cholinergic dysfunction is key in dementia with Lewy bodies (DLB), and likely to influence the cognitive and psychiatric symptoms of this condition. However, patterns of spatial covariance in DLB in terms of nicotinic acetylcholine receptors (nAChRs) is unknown. In this study we used ^{123}I-5-iodo-3-[2(S)-2-azetidinylmethoxy] pyridine (^{123}5IA-85380) SPECT (α4β2 nAChR assessment) to investigate the covariance patterns in DLB and their associations with cognition.
Methods: Fifteen DLB and 16 healthy controls underwent ^{123}5IA-85380 and rCBF (^{99m}Tc-exametazime) SPECT scanning. We applied voxel principal components (PC) analysis, generating a series of PC images representing common intercorrelated voxels across subjects. Linear regression generated specific α4β2 nicotinic and rCBF covariance patterns that contrasted DLB from controls.
Results: A α4β2 pattern that distinguished patients from controls ($F_{1,29}$ = 165.1, p<0.001), showed relative decreased uptake in bilateral temporal pole, inferior frontal, amygdala, olfactory cortex, insula, anterior/mid cingulate and putamen, as well as relative preserved/increased uptake in sensorimotor, fusiform and occipital lobe, implicating regions in a nicotinic receptor expression sense, within limbic, salience, default mode, olfactory, sensorimotor and visual networks. We then successfully derived from patients, α4β2 nicotinic receptor patterns that correlated with $CAMCOG_{total}$ (r=−0.52, p=0.04), MMSE (r=−0.68, p=0.01) and $CAMCOG_{memory}$ (r=−0.70, p=0.01), demonstrating a common 'cognitive' topography of relative decreased binding in lateral/medial prefrontal, lateral temporal, inferior parietal and thalamus along with relative preserved/increased binding in cingulate, insula, occipital and medial temporal regions, structures representing a range of networks supporting executive, language, social cognition, attention and sensory functions.
Conclusion: In conclusion, disease and cognitive related patterns of cholinergic α4β2 nicotinic receptor binding were apparent in DLB and could inform future therapeutic targets of these receptors in this condition.

Clozapine and Risk of Haematological Malignancies: Insights from a Meta-Analysis

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Aims: Clozapine, the first and most effective atypical antipsychotic for schizophrenia, is typically reserved for treatment-resistant cases due to its serious adverse effects. Recent studies have linked clozapine to an increased risk of haematological malignancies (HM). This meta-analysis is the first to systematically investigate this association.
Methods: We performed this study in accordance with the Cochrane Handbook for Systematic Reviews and Meta-analysis of Interventions. Eligible studies included involving patients treated with clozapine, regardless of the primary psychiatric diagnosis, cohort, case-control, cross-sectional that reported the association between clozapine use and the risk of haematological malignancies.
Results: Five studies were included in our meta-analysis (three retrospective cohorts and two case-control studies) involving a total of 211,427 patients. The overall odds of developing HM were significantly higher in the clozapine group compared with the control group (OR=2.1, 95% CI, 1.39–3.18, p=0.00005, I2=83%). Sensitivity analysis was conducted, and heterogeneity was resolved by exclusion of the study by Brainerd et al. The overall effect after its exclusion suggested a significant increase in the odds of HM (OR=2.45, 95% CI, 1.75–3.43, p< 0.00001, I^2=48%). Subgroup analysis showed that the odds of developing leukaemia (OR=4.02, 95% CI, 2.22–7.27, p<0.00001), and lymphoma (OR=6.27, 95% CI, 2.83–13.9, p<0.00001) were significantly higher than the combined risk for all HM. There was no significant association between clozapine and HM with a cumulative dose of <999 defined daily

doses (DDD) (OR=1.11, 95% CI, 0.85–1.46, p=0.44) or 1000–2999 DDD (OR=1.34, 95% CI, 0.76–2.34, p=0.31). However, for patients with a cumulative dose of 3000–4999 DDD and >5000 DDD, the risk of HM was significantly higher in the clozapine group (OR=2.04, 95% CI, 1.46–2.86, p<0.0001), (OR=2.45, 95% CI, 1.32–4.48, p=0.004), respectively. The association between clozapine and haematological malignancies became statistically significant after 5 years of follow-up (OR=2.32, 95% CI, 1.5–3.59, p=0.0002).
Conclusion: Despite the increased risk of HM, clozapine treatment in schizophrenia patients is associated with a significantly lower long-term all-cause mortality rate compared with other antipsychotic use. The small risk should not deter its use or not fuel "clozapine-phobia". The clinical implication of our study is to raise awareness among the psychiatrists about this risk. Haematological abnormalities could be interpreted as typical adverse effects of clozapine, leading to diagnostic bias and delays in malignancy diagnosis.

Efficacy and Safety of Ondansetron in Schizophrenia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Aims: It has been shown that 5-hydroxytryptamine3 (5-HT3) receptors are involved in the pathogenesis of schizophrenia. This systematic review and meta-analysis of randomized clinical trials (RCTs) evaluates the efficacy and safety of ondansetron, a potent 5-HT3 receptor antagonist, as adjunctive treatment for the management of schizophrenia, especially the negative symptoms and cognitive deficits.
Methods: A comprehensive search of electronic databases, including PubMed, Scopus, Cochrane, and Web of Science, was performed in October 2024. We included only randomized controlled trials (RCTs), and their data were extracted and analysed using RevMan 5.4 software. The primary outcome was the PANSS (Positive and Negative Syndrome Scale) negative subscale.
Results: Eight RCTs involving 533 patients were included in the study. Ondansetron showed a statistically significant improvement in PANSS negative subscale at 12 weeks [pooled as mean difference, MD=−2.96, 95% CI [−4.69, −1.24], p=0.00007] and in general psychopathology scale [MD= −2.71, 95% CI [−3.52, −1.90]] compared with placebo. However, ondansetron and placebo did not differ in reduction of PANSS positive subscale [MD= 0.1, 95% CI [−1.19, 1.38], p=0.88], and depression scale (SMD= 0.71, 95% [−0.35, 1.77], p=0.19). Ondansetron showed no significant difference regarding tardive dyskinesia between the two groups. However, constipation was significant in the ondansetron group over placebo.
Conclusion: The study's findings support the use of ondansetron as adjuvant therapy in the management of schizophrenia, particularly the negative symptoms and cognitive deficits.

Efficacy and Safety of Pentoxifylline in Major Depressive Disorder: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Aims: Major depressive disorder (MDD) may be linked to broader pathophysiological pathways such as oxidative stress, inflammation, vascular dysfunction, and neuroplasticity alterations. Pentoxifylline (PTX), a pleiotropic drug, targets all these pathways through non-specific phosphodiesterase (PDE) inhibition. This is the first systematic review and meta-analysis to examine the role of PTX in major depressive disorder.
Methods: A comprehensive search of electronic databases, including PubMed, Scopus, Cochrane, and Web of Science, was performed in October 2024. We included only randomized controlled trials (RCTs), and their data were extracted and analysed using Reman 5.4 software. The inclusion criteria as follows: adult patients diagnosed with MDD were included as the population. The intervention considered was pentoxifylline, either alone or in combination with selective serotonin reuptake inhibitors. Comparators included placebo, either alone or combined with SSRIs. Eligible studies needed to report outcomes such as the Hamilton Depression Rating Scale (HAM-D).
Results: Four RCTs with 318 patients were included in the study. PTX showed a statistically significant improvement in HAM-D scores at the primary endpoint compared with the placebo (MD= −3.84, 95% CI [−4.87 to −2.81], p<0.00001). Moreover, PTX showed a statistically significant increase in serotonin and BDNF levels (MD=20.76 ng/mL, 95% CI [5.49 to 36.04], p=0.008; and MD=10.83 ng/mL, 95% CI [−0.22 to 21.88], p=0.05, respectively) and a statistically significant decrease in TNF-α and IL-6 levels (MD=−3.24 pg./mL, 95% CI [−4.12 to −2.36], p<0.00001; and MD= −2.64 pig/mL, 95% CI [−3.79 to −1.48], p<0.00001, respectively). There was no statistically significant difference between the PTX and placebo in any of the reported side effects including nausea, vomiting, headache, diarrhoea, increased appetite, and sexual dysfunction.
Conclusion: The study findings suggest that PTX may be effective and safe as an adjuvant antidepressant agent in patients with MDD, demonstrating a significant reduction in HAM-D scores. The results of this study need to be interpreted with caution considering several limitations.