Psychiatry Research Review™

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Issue 41 – 2016

In this issue:

Abbreviations used in this issue
DDD = daily defined dosage
HR = hazard ratio
LAI = long-acting injectable

Winner of the NZMA Anatomy Prize Draw is Piotr Gawor.
The prize is a $300 Prezzy Card.

Welcome to issue 41 of Psychiatry Research Review.

A comprehensive systematic review and meta-analysis of randomised controlled trials demonstrates that long-acting injectable antipsychotics have a generally acceptable safety profile. In another couple of studies that we discuss in this issue, the evidence suggests that antipsychotics must be used with great care in older people, especially in those with dementia. We also comment upon results indicating that mood disorder risk in young adults is transmitted both genetically and via childhood abuse/neglect as a mediator. These findings have profound implications for risk identification and also the prevention of mood disorder in the next generation.

We hope you find this issue useful for your daily practice and we welcome any comments or feedback.

Kind regards,

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Adverse renal, endocrine, hepatic, and metabolic events during maintenance mood stabilizer treatment for bipolar disorder: a population-based cohort study

Authors: Hayes JF et al.

Summary: This investigation into adverse event rates during maintenance mood stabiliser treatment involved patients with bipolar disorder taking lithium (n=2148), valproate (n=1670), olanzapine (n=1477), or quetiapine (n=1376) between 1 January 1995 and 31 December 2013. The median duration of drug treatment was 1.48 years. In analyses adjusted for propensity score, age, and calendar year, that accounted for clustering by primary care practice, rates of chronic kidney disease stage ≥3 were lower with valproate, olanzapine, and quetiapine than with lithium. Rates of hypothyroidism, new-onset hyperthyroidism and hypercalcaemia were lower with valproate and olanzapine than with lithium. However, valproate, olanzapine and quetiapine were more likely to result in >15% weight gain when compared with lithium; the rate of new-onset hypertension was also higher in those treated with olanzapine, compared to those on lithium. There were no significant between-group differences in rates of chronic kidney disease stage ≥4, type 2 diabetes, cardiovascular disease, or hepatotoxicity.

Comment (DM): Treatment options for prophylaxis of bipolar disorder have been compared regarding efficacy, as previously described in Research Review. This UK cohort study is the first with adequate power to systematically compare these options in terms of adverse effects. Although the study abstract is bedevilled by a distracting excess of statistics, the results are nonetheless clear and compelling. One finding was not particularly surprising, with lithium's known renal and endocrine toxicity being well demonstrated. On the other hand, both valproate and the two second-generation antipsychotics (olanzapine and quetiapine) were clearly more likely to promote significant weight gain. Had the study continued for longer, it seems likely that this would have resulted in worse diabetic and cardiovascular (and possibly mortality) outcomes as well. A further study to verify this important point is required.

Reference: PLoS Med. 2016;13(8):e1002058

Abstract

Royal Australian and New Zealand College of Psychiatrists (RANZCP)

Royal Australian and New Zealand College of Psychiatrists (RANZCP) CPD Program participants can claim one credit per hour under 'Category 4 - Self Guided Learning' (minimum 20 credits per year). Research Reviews can be included as 'Self-Guided Learning'

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Childhood trauma, family history, and their association with mood disorders in early adulthood

Authors: Jansen K et al.

Summary: This investigation tested the hypothesis that childhood trauma is a mediating factor for the association between family history of mood disorder and mood disorder in adulthood. Young adults with bipolar disorder or major depressive disorder and matched controls without any mood disorder were administered the Childhood Trauma Questionnaire. All types of trauma were associated with both major depression and bipolar disorder, whereas sexual abuse was only associated with bipolar disorder. An assessment of the extent to which trauma mediates the association between family history and diagnosis of any mood disorder revealed that family history of psychiatric illness was also associated with mood disorder in adulthood and with childhood trauma. Using the presence of any mood disorder as the outcome, a third of the effect of having any family history of mood disorder was mediated via childhood trauma.

Comment (DM): This remarkable study, set in the far south of Brazil, addresses fundamental questions about the mechanisms by which mood disorder risk is transmitted. Although cross-sectional in design, and thus unable to conclusively demonstrate causality, the investigation strongly suggests that mood disorder risk in young adults is transmitted both genetically and via childhood abuse/neglect as a mediator. If verified in longitudinal studies, this finding is profoundly significant with respect to not only risk identification but also primary prevention (or at least mitigation) of mood disorder in the next generation. The role of epigenetics is also suggested as a further mechanism worthy of exploration in other studies. For those interested in a wider discussion, an accompanying editorial in the same journal (2016;134:279–80) is recommended.

Reference: Acta Psychiatr Scand. 2016;134(4):281-6
Abstract

Offspring of depressed parents: 30 years later

Authors: Weissman MM et al.

Summary: Data are presented from 30 years of follow-up of 147 biological offspring (mean age 47 years) of depressed (high-risk) and nondepressed (low-risk) parents. The risk for major depression was ~3-fold higher in the high-risk cohort. In both groups, the period of highest risk for first onset was between ages 15 and 25. Prepubertal onsets were uncommon, but the risk was >10-fold higher among high-risk offspring. The early onset of major depression among the offspring of depressed parents was not offset by later first onsets in the low-risk group as they matured. The increased rates of major depression in the high-risk group were largely accounted for by the early onsets, but later recurrences in the high-risk group were significantly increased. The high-risk offspring continue to have overall poorer functioning and receive more treatment for emotional problems. The high-risk group had increased mortality (5.5% vs 2.5%) due to unnatural causes, with a nearly 8-year difference in the mean age at death (38.8 years vs 46.5 years).

Comment (DM): This remarkable longitudinal study provides a useful and interesting counterpoint to the preceding cross-sectional investigation (above), which identified the role of abuse and neglect as mediating a substantial part of the increased risk of mood disorders in the next generation. The present study takes a different approach and, with careful methodology and robust statistics, identifies the temporal pattern of increased incidence over 3 decades of follow-up. In addition to concentrated risk in early adulthood, the study also identifies significant elevations of social dysfunction and premature mortality in the at-risk group. The implications for clinical practice are unsurprising but still noteworthy; this report validates the importance of routine enquiry into family psychiatric history, and emphasises the relevance of careful follow-up of biological relatives of patients with major mood disorders.

Reference: Am J Psychiatry. 2016;173(10):1024-32
Abstract

Increased mortality among people with anxiety disorders: total population study

Authors: Meier SM et al.

Summary: These researchers used nationwide Danish register data with over 30 million person-years of follow-up to assess mortality risk in people with anxiety disorders. Over a mean 9.7-year follow-up, 1066 (2.1%) people with anxiety disorders died. Compared with the general population, individuals with anxiety disorders had a significantly higher risk of death by natural and unnatural causes (natural mortality rate ratio [MRR] 1.39; 95% CI, 1.28 to 1.51; unnatural MRR 2.46; 95% CI, 2.20 to 2.73). Of those who died from unnatural causes, 16.5% had comorbid diagnoses of depression (MRR 11.72; 95% CI, 10.11 to 13.51).

Comment (DM): By using the entire population of Denmark in the sampling frame, together with careful statistical control of potential confounders, these investigators were able to show a convincing deleterious effect of anxiety disorders on mortality. Of particular interest was the more marked effect on death from unnatural causes (accidents, suicide, homicide), and a dose-response relationship with either multiple anxiety disorders, or anxiety with comorbid depression. By contrast, a somewhat more modest (but still significant) increased risk of death from natural causes associated with anxiety disorders was largely attributable to the effects of comorbid substance use, notably alcohol and tobacco. What does this mean for clinical practice? Because of their prevalence, these disorders need to be reckoned as a cause not just of reduced quality-of-life and impaired social function, but also of premature mortality. It will be of interest to compare the population 'mortality gap' contribution of common mental disorders, including anxiety, with the recognised major effects of schizophrenia, bipolar disorder, and severe substance abuse.

Reference: Br J Psychiatry. 2016;209(3):216-21
Abstract

Independent commentary by Associate Professor David Menkes, an academic psychiatrist with a background in psychology and pharmacology (PhD 1983, Yale). Since completing specialist training in Dunedin (FRANZCP 1989) he has worked as an academic liaison psychiatrist in NZ and the UK. He has a continuing interest in the pharmacology and toxicology of drug treatments in psychiatry, is a member of the Medicines Adverse Reactions Committee (Medsafe), the PTAC Mental Health Subcommittee that advises PHARMAC, www.healthyskepticism.org, and works closely with the International Society of Drug Bulletins (www.isdbweb.org).

Independent commentary by Associate Professor Wayne Miles, a psychiatrist with Waitemata DHB, Clinical Director of Awhina Research and Knowledge, and a Clinical Associate Professor with Auckland University School of Medicine. He has had many roles with the RANZCP including that of President, and has also been involved with NZMA. Wayne has had extensive experience in both the treatment of, and research into schizophrenia. He has conducted sponsored research with, and/or received honoraria for services to Otsuka, Pfizer, Roche, Eli Lilly, Janssen, Amgen, Bristol Myers Squibb and GSK.

A quasi-randomized feasibility pilot study of specific treatments to improve emotion recognition and mental-state reasoning impairments in schizophrenia

Authors: Marsh PJ et al.

Summary: This Australian-based research investigated the acceptability, feasibility and limited efficacy of two programs designed to improve social cognition in schizophrenia: the SoCog Mental-State Reasoning Training (SoCog-MSRT) and a newly developed SoCog Emotion Recognition Training (SoCog-ERT) program. Thirty-one people with schizophrenia or schizoaffective disorder were allocated to either SoCog-MSRT (n=19) or SoCog-ERT (n=12); each 6-week program consisted of 12 twice-weekly 1-hour sessions. Participants were assessed on social cognition, neurocognition and symptoms at baseline, post-training and at 3 months after completing training. Attendance was high for both programs (an average of 89.29% with SoCog-MSRT and 85.42% with SoCog-ERT). Participants rated both programs as enjoyable and beneficial. In both groups, scores were increased on a false belief reasoning task and the Reading the Mind in the Eyes test. The SoCog-MSRT group also showed reduced personalising attributional biases in a small number of participants, while the SoCog-ERT group showed improved emotion recognition.

Comment (WM): Psychiatrists will be increasingly aware of the importance of the cognitive impairments of schizophrenia as a prime predictor of the impact of the disorder on function. Inability to correctly judge what another is thinking and feeling makes it very difficult to have successful relationships. This paper focusses on the impairments of social cognition and explores possible intervention methods to help offset the impacts of these deficits.

The authors provide a comprehensive review of types of training methods to assist development of new skills. I therefore recommend it to anyone wanting to know more about the background thinking. They report a carefully designed study to examine two kinds of intervention, one that is based on theory of mind and attribution style without specific reference to emotion recognition and a second that has strong elements of emotion recognition training.

The study design was to be a randomised controlled trial that had both active control treatment in the form of social activities and a wait list non-active control. They found, however, that both referrers of subjects and the subjects themselves were not prepared to be involved in the control groups. This calls in to question the wisdom of designing larger trials with an RCT design. The authors suggest a better alternative might be a personalised treatment protocol with allocation on predetermined characteristics that looks at at within subject differences across time. The study objectively measured the participants' interest in and enjoyment of the activity with encouraging results. They found that attendance rates were high (in the mid-80% range). They describe a battery of testing that sounds quite onerous, but it seems most participants were OK with it. Though the numbers studied did not allow definitive conclusions about the ability of the training to induce positive shifts there were very encouraging results that strongly support ongoing exploration of social cognition training.

This paper does not have results that inform clinicians about the significance of the training for outcome in schizophrenia. Though the paper is not the easiest read it does provide a useful insight into a potential area for future treatment and will also assist those who are planning to research the area.

Reference: BMC Psychiatry. 2016;16(1):360
Abstract

Mortality risk associated with long-acting injectable antipsychotics: a systematic review and meta-analyses of randomized controlled trials

Authors: Kishi T et al.

Summary: This systematic review was performed in response to safety concerns during the early postmarketing vigilance phase of long-acting injectable (LAI) antipsychotics in Japan. Three categorical meta-analyses of randomised controlled trials (RCTs) compared all-cause death (primary outcome) and death due to suicide among patients with schizophrenia: individual and pooled LAI antipsychotics vs placebo, individual and pooled LAI antipsychotics vs oral antipsychotics (OAPs), and head-to-head comparisons of LAI antipsychotics. The analysis included 52 RCTs (53 comparisons; total participants = 17,416, LAI antipsychotics = 11,360, OAP = 3910, and placebo = 2146; mean study duration: LAI antipsychotics vs placebo = 28.9 weeks, LAI antipsychotics vs OAPs = 64.5 weeks). No between-group differences were observed between placebo and the pooled or individual LAI antipsychotics (aripiprazole, fluphenazine, olanzapine, paliperidone, and risperidone) regarding the incidences of all-cause death (pooled LAI antipsychotics: risk ratio [RR] 0.64; p=0.37) and death due to suicide (pooled LAI antipsychotics: RR 0.98; p=0.98). However, a subgroup meta-analysis of short-duration RCTs (≤13 weeks) showed a trend toward a lower incidence of all-cause death with pooled LAI antipsychotics versus placebo (RR 0.29; p=0.08). Pooled LAI antipsychotics (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, risperidone, and zuclopenthixol) did not differ from pooled OAPs regarding all-cause death (pooled LAI antipsychotics: RR 0.71; p=0.30) or death due to suicide (pooled LAI antipsychotics: RR 0.94; p=0.91). Individual LAI antipsychotics and OAPs were associated with similar risks of death. There were insufficient data for head-to-head comparisons of individual LAI antipsychotics.

Comment (DM): The decision to use LAI antipsychotics is usually prompted by nonadherence to prescribed oral medication. As such, the decision is often resisted by the patient and sometimes compelled by the Mental Health Act. Accordingly, the perceived effectiveness and acceptability of LAI is a very important feature, both for clinicians and for patients and their families. Indeed, persuading patients to continue with LAI antipsychotics can be something of a mission, and can be undermined by the popular press and other media that emphasise our pharmacotherapies and sometimes refer to "toxic psychiatry". This carefully conducted meta-analysis will provide reassurance to mental health teams, and prescribers in particular, that depot medications have a generally acceptable safety profile.

Reference: Schizophr Bull. 2016;42(6):1438-45
Abstract

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Antidepressants and mortality risk in a dementia cohort: data from SveDem, the Swedish Dementia Registry

Authors: Enache D et al.

Summary: These researchers analysed data from the Swedish Prescribed Drug Register on antidepressants dispensed at the time of dementia diagnosis and during the 3-year period before dementia diagnosis in 20,050 memory clinic patients diagnosed with incident dementia. During a median 2-year follow-up from dementia diagnosis, 25.8% of dementia patients died. One-quarter (25.0%) of patients were on antidepressants at the time of dementia diagnosis, while 21.6% used antidepressants at some point during a 3-year period before a dementia diagnosis. Use of antidepressant treatment for 3 consecutive years before a dementia diagnosis was associated with a lower mortality risk for all dementia disorders and in Alzheimer's disease.

Comment (WM): This Swedish report addresses an important question for psychiatrists who work with older people. It notes that antidepressants are commonly used in people developing dementia but that the published evidence for their use is inconsistent. Several studies support a benefit, but a Cochrane review says they are not effective.

The study looks at a cohort of people registered with the Swedish Dementia Register from 1 May 2007 to 31 October 2013. The cohort is restricted to those registered at memory clinics because of diagnostic inconsistency in primary care. 20,050 patients were included. Data regarding the prescribing and dispensing of medication, including antidepressants, was obtained by matching the patient's unique identifier in the two registers. Data was taken at four time points, one year after the diagnosis of dementia and in the first, second and third year prior to diagnosis. Data was assembled on deaths in the cohort from the Swedish population register.

The paper analyses in considerable depth relationships between antidepressant types, time course of prescription and types of dementia in a way that is very informative but too extensive to cover here. The major finding was support for a reduction in mortality in dementia, particularly Alzheimer's type, when antidepressants were used in the prodromal stage.

Reference: Acta Psychiatr Scand. 2016;134(5):430-40
Abstract

Are mental health services getting better at responding to abuse, assault and neglect?

Authors: Read J et al.

Summary: This audit of files from 250 clients attending four New Zealand mental health centres examined whether staff responses to abuse disclosures had improved since the introduction of a trauma policy and training programme. It identified that a significantly greater proportion of abuse cases were included in formulations and treatment plans, compared with an audit undertaken prior to the programme. However, the proportion referred for relevant treatment remained at <25% across abuse categories. Response rates for neglect disclosures were significantly lower than for abuse cases. Fifty percent of the files in which abuse/neglect was recorded noted whether the client had been asked about previous disclosure, and 22% noted whether the client thought there was any connection between the abuse/neglect and their current problems. Fewer than 1% of cases were reported to legal authorities. People diagnosed with a psychotic disorder were significantly less likely to be responded to appropriately.

Comment (WM): This paper presents the result of a New Zealand-based case note audit. A literature review is presented that highlights high rates of association of childhood abuse and neglect with later psychiatric diagnosis and treatment. It is claimed that identification of and/or action on these abuse experiences suggest a high rate of under-reporting. The study makes use of a previously conducted audit at an Auckland CMHC (1997) that was conducted before the DHB introduced a new best practice recommendation regarding inquiry into and response made to abuse and trauma history (2000).

The researchers looked at 250 files of adult users of four CMHCs in the ADHB area. It is not clear what the time frame for the inclusion was; files were started after Jan 1 2001 but I cannot see when the list was generated, thus the end cut-off date is unclear. We are told the list of 250 was "generated at random", but not told how nor what percentage of the CMHC clients this represented. From the summary description, it seems the researchers had a well-developed data collection form but less clear was how operationalised the categories were. An extensive search through available records was made. The brief demographics given are consistent with what one would expect in an urban CMHC. There is analysis of different types of abuse and neglect that are beyond the scope of the review. Key findings of the study are that abuse or neglect was recorded in 56% of files, and that inclusion in formulations had significantly improved. Inclusion in treatment plans, especially for child sexual abuse had risen (now at 44%), as had referral for relevant treatment. Two facets that are highlighted by the paper are the continuing low rate of reporting to legal authorities and the very large effect of a diagnosis of a psychotic condition; these people are much less likely to have reports responded to compared to those with depression. Overall, the authors point to a positive change in recognition and response, but see considerable gains yet to be made.

Reference: Acta Psychiatr Scand. 2016;134(4):287-94
Abstract

Cumulative dosages of antipsychotic drugs are associated with increased mortality rate in patients with Alzheimer's dementia

Authors: Nielsen RE et al.

Summary: In this study, 45,894 patients with Alzheimer's disease were followed for 3,803,996 person-years in total; 27,894 deaths were recorded. Cumulative antipsychotic exposure increased mortality: >0 daily defined dosage (DDDs) but <90: HR 2.20 (95% CI, 2.14 to 2.27; p<0.001); ≥90 DDDs but <365: HR 1.81 (95% CI, 1.74 to 1.89; p<0.001); ≥365 DDDs but <730: HR 1.38 (95% CI, 1.428 to 1.49; p<0.001); and ≥730 DDDs: HR 1.06 (95% CI, 0.95 to 1.18; p=0.322), when controlling for proxy markers of severity, somatic and mental comorbid disorders.

Comment (WM): The authors note increased mortality in Alzheimer's disease as well as an observed increase in mortality where antipsychotic treatment has occurred. They comment on the lack of evidence for positive effects of antipsychotics in Alzheimer patients with behavioural and psychological symptoms of dementia and the absence of consideration of the balance of negative and positive effects.

A national (Danish) retrospective cohort study was designed that utilised national databases to examine whether cumulative and or current exposure to antipsychotic drugs increased mortality in people with Alzheimer's.

The cohort was all diagnosed with Alzheimer's disease or prescribed antidementia drugs during the period Jan 1 2000 to Dec 31 2011. The data of primary interest was medication. That relating to antipsychotic prescription was coded to look at current exposure (based on amount in past year) and cumulative doses from the date of first dementia diagnosis. The authors report a defined daily dose (DDD) that subdivides into four groups; I am unclear, however, exactly how they derived that DDD. They gathered secondary data on factors that might be confounders, including severity of disease, psychiatric comorbid disorder, somatic comorbid disorder and cardiovascular risk factors. As the databases did not contain exact measures of many of these covariates, the authors used proxy indicators (well described in the paper). Primary data analysis was a regression analysis with all-cause mortality as the primary outcome against cumulative and current exposure. These were adjusted for the covariates described above. They conducted a secondary analysis with only cumulative drug dosage. The analytic processes and assumptions seem fine to a non-expert.

The overall cohort was an impressive 45,894 patients and median follow-up time per person was 82.89 years. Overall, they found a decrease in mortality for females and for those with an older age at diagnosis. 18,094 patients were exposed to antipsychotic medication. Current antipsychotic exposure increased mortality at a rate of 2.28. As there was an association between current and cumulative exposure, a secondary analysis was performed, which showed cumulative doses increasing mortality. This persisted after adjustment for the other explanatory variables (other medication, severity and comorbid conditions, which all had links to increased risk).

The authors note a number of limitations and consider ways in which factors might confound the findings. For example, it is possible that more severely ill patients are prescribed antipsychotics. It is interesting though that the highest DDD showed a drop in the risk of mortality. This could be explained by a survival bias; those who get the longest exposure to the antipsychotic have survived the initial exposure. Despite the possible confounders, I believe this study has sufficient merit for its results to add to the increasing voice for extreme caution in using antipsychotic medications in people with dementia.

Reference: Acta Psychiatr Scand. 2016;134(4):314-20
Abstract

Antipsychotic drugs and risk of hip fracture in people aged 60 and older in Norway

Authors: Bakken MS et al.

Summary: This analysis involved 906,423 Norwegians aged ≥60 years, 39,938 (4.4%) of whom experienced a primary hip fracture. Information was obtained on all prescriptions of antipsychotic drugs dispensed from 2004 to 2010 (Norwegian Prescription Database) and data on all primary hip fractures from 2005 to 2010 (Norwegian Hip Fracture Registry). Greater risk of hip fracture was associated with exposure to any antipsychotic (standardised incidence ratio [SIR] 2.1; 95% CI, 1.9 to 2.1), first-generation antipsychotics (FGAs) (SIR 2.0; 95% CI, 1.8 to 2.2), second-generation antipsychotics (SGAs) (SIR 2.2; 95% CI, 1.9 to 2.4), prolactin-sparing antipsychotics (SIR 2.4; 95% CI, 1.8 to 3.1) and prolactin-elevating antipsychotics (SIR 2.0; 95% CI, 1.9 to 2.2).

Comment (WM): This is another recent report that psychiatrists need to take in to account when considering using antipsychotic agents in the elderly and perhaps particularly in those with behavioural and psychological symptoms of dementia.

The paper notes that hip fractures are common in older people and reviews possible risk factors for such fractures. Psychotropic drugs are noted to be an independent (and modifiable) factor. The high use of antipsychotics in those with behavioural symptoms of dementia is recognised. A number of possible mechanisms for higher rates of fracture including effects on prolactin, effects on sex hormones and direct metabolic interference with bone are summarised. The study utilised the Norwegian databases of the general population, of prescription data and the Hip Fracture Registry. A limitation of the Prescription Database is that it does not include information relating to people in hospitals or nursing homes. A possible limitation of the Hip Fracture Database is that it only includes those undergoing surgery; one assumes if people die before surgery they would not be identified as having had a fracture. The study is carefully designed, taking as its primary cohort all those who are on the Norwegian population database being born before 1945, living in Norway on January 1 2005. Medication exposure is analysed using the Prescription Database and any exposure to an antipsychotic is recorded. There is a full recording of type, dose and duration. The authors rightly caution they cannot be sure what the actual daily dose was, but attempt to make reasonable estimates. They are particularly interested in overall and recently started exposures. The study population was 905,422 people. 8% of the study population was exposed to antipsychotic drug prescription during the study period. 4.4% of the total population experienced a hip fracture. The risk of a hip fracture was greater in people exposed to any antipsychotic drug (a little over twice as likely). The risk was greater for exposed (to antipsychotic) men than women. The study did not show a significant difference in risk of fracture for type of antipsychotic (FGA, SGA, prolactin-sparing or prolactin-elevating). People who had recently started antipsychotic drug were at an elevated risk compared to the overall exposure group.

This article and the previous must sound a very large word of caution for any psychiatrist contemplating treating older people with antipsychotics, especially where there is a likelihood of dementia.

Reference: J Am Geriatr Soc. 2016;64(6):1203-9
Abstract