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How does industry-sponsored education market overdiagnosed conditions? A cohort study of depression, osteoporosis and overactive bladder events in Australia

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Contributors: BM initiated the study, designed the data coding approach and plans for analysis, assisted with the development of the coding scheme, carried out analyses, and drafted and revised the paper. She is the guarantor. SW and AF contributed to the study design and coding scheme, carried out data coding and analysis, and revised the draft paper; QG, RM and LB contributed to the study design and coding scheme and revised the draft paper.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). Dr. Mintzes reports that she was an expert witness on behalf of plaintiffs in a Canadian class action suit concerning cardiovascular risks of a testosterone gel. None of the other authors report any financial relationships with organisations that might have an interest in the submitted report in the previous three years. None of the authors have received any financing from pharmaceutical manufacturers. The authors declare no other relationships or activities that could appear to have influenced the submitted work.

Transparency: As guarantor, Dr Mintzes affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Abstract: [300 words]

Objectives: to investigate patterns of industry sponsored educational events that focus on specific health conditions for which there are concerns about overdiagnosis.

Design and Setting: This retrospective cohort study examines publicly reported industry-sponsored events in Australia from October 2011 to September 2015 for three conditions potentially subject to overdiagnosis: depression, osteoporosis, and overactive bladder. We used a database of transparency reports to identify events with a focus on depression, osteoporosis and overactive bladder and compared these with other sponsored events. We hypothesised that companies marketing treatments for each condition would sponsor related events and that target audiences would mainly work in primary care, reflecting a broad patient population.

Main outcome measures: Event and attendee characteristics, sponsoring companies, related marketed treatments, cost-effectiveness ratings and dispensing rates.

Results: Over the study period, we identified 3,132 events: 1,567 events focusing on depression, 1,375 on osteoporosis and 190 on overactive bladder, with a total of 96,660 attendees. These condition-focused events included more dinners than other sponsored events, and were more often attended by primary care doctors: relative risk (RR) = 3.06 (95% CI 2.81 – 3.32) for depression, RR= 1.48 (95% CI 1.41-1.55) for osteoporosis, and RR= 2.59 (95% CI 2.09-3.21) for overactive bladder. Servier, which markets agomelatine and AstraZeneca (quetiapine) sponsored 51.2% and 23.0% of depression events respectively. Amgen and GSK, which co-market denosumab, sponsored 49.5% of osteoporosis events, and Astellas and CSL (mirabegron and solifenacin) sponsored 80.5% of overactive bladder events.

Conclusions: Industry sponsorship of education on depression, osteoporosis and overactive bladder focused on primary care and was concentrated among few companies that market medicines for each condition. These products are subject to efficacy, safety and cost-effectiveness concerns, raising questions about the focus of sponsored education.

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Strengths and limitations of this study

- Australia's transparency reports of industry funding of health professionals were unique internationally until 2015, in that the focus was on sponsored events.
- This is the first data-driven national analysis of condition-specific industry educational event sponsorship for overdiagnosed conditions.
- Classification of events was blinded to sponsor, attendee characteristics, and event descriptions.
- For each condition, we examined trends over time in sales and dispensing of lead sponsors' relevant marketed drugs, but we could not assess causal links between increased prescribing and event attendance, as no information was publicly available on the identity of individual event participants.
- Limited detail was available on the content of sponsored events; therefore, despite a sensitive search, we may have missed some relevant events per condition

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Introduction

The role of pharmaceutical industry sponsorship of health professional education has been subject to considerable controversy. There is disagreement about whether sponsored education is primarily promotional or educational. It has been described on the one hand as, "marketing masquerading as education", (1) and on the other, if accompanied by proper controls, as able to meet the goal of, "needs based, relevant, accessible education that is balanced and unbiased and improves health care outcomes." (2)

This controversy extends not only to how treatment outcomes are discussed, but also to how conditions are defined. Messages in commercially-sponsored education may exaggerate prevalence and/or attempt to medicalise aspects of ordinary life. Identified "marketing messages" in continuing medical education (CME) for low female sexual desire included statements that it is "very common and underdiagnosed", and that, "women may not be aware that they are sick or distressed." (3) Similarly, United States (U.S.) CME sponsored by a testosterone manufacturer supported a broader definition of hypogonadism than in listed indications for testosterone. (4)

A sponsored CME campaign can reach many health professionals, with potential widespread effects on practice. Purdue Pharma's launch of the opioid analgesic oxycodone in the U.S. included over 20,000 sponsored educational events, many of which targeted GPs, potentially contributing to more opioid use in primary care. (5)

These are product-specific examples of sponsored CME that received media attention and may not reflect broader trends. There has been little exploration of the link between sponsored CME and specific conditions prone to overdiagnosis. Overdiagnosis, the detection of conditions unlikely to lead to ill-health, disability or death in the absence of treatment, has been characterised as a "modern epidemic". (6, 7) It can lead to harm from adverse effects of treatments from which a person is unlikely to benefit, to psychological harm if a healthy person suffers from anxiety or stigma due to disease labelling, and to harm to society through higher healthcare costs. There is evidence of commercial influence on overdiagnosis in a range of conditions, through direct and indirect marketing aiming to establish the need for a product. (7)

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National patterns of industry sponsorship can shed light on controversies concerning the role of sponsored CME. From 2007 to late 2015, members of Medicines Australia, the national pharmaceutical industry trade association, were required by law to report on sponsored events for health professionals. (8) These data provide a unique opportunity to examine the link between condition-specific sponsored events and companies marketing medicines for a condition.

We report here on event sponsorship with a focus on three conditions highlighted in the medical literature as potentially subject to overdiagnosis: depression, (9) osteoporosis (10), and overactive bladder. (11)

We hypothesise that companies marketing drugs for depression, osteoporosis, or overactive bladder are more likely to sponsor events with a focus on that condition than other companies. We also hypothesise that these events tend to target a primary care audience, reflecting milder disease states. To investigate clinical implications, we examine whether sponsors' products were judged to be cost-effective and are covered under Australia's Pharmaceutical Benefits Scheme's (PBS). We assess sponsorship patterns per condition in terms of audience, clinical versus non-clinical setting, provision of meals, and timing in relation to when a company had a product for sale.

Methods

Data sources

We downloaded 301 publicly available company reports covering the period October 2011 to September 2015 from the Medicines Australia website (www.medicinesaustralia.com.au), converted them from PDF into Excel files, cleaned the data and resolved discrepancies. These reports include the sponsoring company, timing, event description, venue type, number and profession of attendees, hospitality costs and total event costs. Coding methods are described in detail elsewhere. We developed a retrospective cohort of sponsored events based on timing of sponsorship per company over time. (12) The data set used for this analysis is available at: http://dx.doi.org/10.4227/11/592631edbd9d5

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We obtained a list of brands sold in Australia for each condition from the Australian Medicines Handbook (13) and manufacturers' websites, and annual dispensing data for publicly reimbursed drugs through Australia's Pharmaceutical Benefit Scheme (PBS) http://www.pbs.gov.au/info/browse/statistics#AS. For non PBS-subsidised drugs, sales volume data were obtained through QuintilesIMS.

We examined volume of use using annual numbers of dispensed prescriptions for PBS-subsidised drugs and numbers of units sold to retail and hospital pharmacies for non PBS-subsidised drugs.

Selection of targeted conditions

We chose depression, osteoporosis, and overactive bladder as illustrative case studies of conditions for which diagnostic thresholds and treatment have extended beyond levels at which patients are likely to benefit. We selected these conditions *a priori* before carrying out any analyses.

Depression screening leads to many false positives, (14) (15) and many patients prescribed antidepressants in primary care fail to meet diagnostic criteria for major depression, (16) a phenomenon that has been described as "medicalising sadness". (9) In 2013, Australia had the second highest rate of antidepressant use among OECD countries. (17)

Questions have also been raised about diagnostic criteria for osteoporosis. Bone density screening is poorly predictive of clinical fractures, and a focus on bone density rather than fragility fractures has led to many more diagnoses. (10) Further treatment expansion has occurred through lowered thresholds for "pre-osteoporosis" and "osteopenia".

An "imprecise" symptom-based definition of overactive bladder, largely linked to commercial interests, has replaced urodynamically confirmed bladder instability. (11) Tolterodine, marketed by Pharmacia, was the first drug approved for overactive bladder symptoms. In 2002, Pharmacia's Vice-President described a threefold expansion of the treatable population through a definition of overactive bladder no longer requiring urinary incontinence. (18)

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Coding of Medicines Australia data on sponsored events

An initial coding scheme for industry-sponsored events included sponsoring company, location, attendee profession, clinical focus, type of hospitality, and a set of relevant keywords to search unstructured text. (12) We designed an additional coding scheme to identify events focusing on the three included conditions. The research team iteratively developed keywords based on disease names/symptoms and drug classes and products sold in Australia (generic and brand names) for each condition. Keywords were used to search unstructured text in the "Description of function" column of reports. All relevant keywords associated with ≥ 1 event listed in the database were retained in the final coding scheme. (On-line Appendix, Table 1) During coding, we concealed other variables (using Excel's 'Column Hide' function) to blind the coder [SS] to sponsor, attendee characteristics, and event descriptors.

Analysis

For each included condition, we provide a detailed analysis for all companies sponsoring at least 5% of events. We examined whether these companies market drugs to treat the condition, and PBS reimbursement status for these drugs. We present frequency tables for event and attendee characteristics. Costs are reported in AUD$. We performed chi square analyses to compare events per condition with other sponsored events using SPSS-Version 22.

Results

Over the 4-year study period, we identified 3,132 events focusing on the three conditions, with 96,620 attendees. This was 1,567 events with a focus on depression, with 41,474 attendees; 1,375 on osteoporosis with 33,916 attendees; and 190 on overactive bladder with 21,270 attendees. As no individuals are named, we could not ascertain numbers of repeat attendees. Table 1 summarises event characteristics. Events focusing on these conditions represent 2.7% of sponsored events (n=116,845) over the 4-year period, and 2.8% of attendees (n=3,481,750).

For all three conditions, the median number of event attendees (19-20) was similar to sponsored events in general (12). However, attendees were more likely to be primary care physicians (GPs or family medicine) than at other events: relative risk (RR) = 3.06 (95% CI 2.81 – 3.32) for

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depression, RR= 1.48 (95% CI 1.41-1.55) for osteoporosis, and RR= 2.59 (95% CI 2.09-3.21) for overactive bladder. Depression and osteoporosis events were also more likely to feature a dinner than other events: RR= 1.73 (95% CI 1.64-1.82) for depression and RR = 1.33 (95% CI 1.27-1.38) for osteoporosis. This trend was not seen for overactive bladder. For all three conditions, events were less often held in a clinical setting (hospital or clinic) than other sponsored events: RR = 0.51 (95% CI 0.50-0.53) for depression; RR = 0.72 (95% CI 0.68-0.76) for osteoporosis; RR= 0.47 (95% CI 0.43-0.50) for overactive bladder.

The median cost per attendee was higher than for events in general (AUD$14): AUD$104 for depression, AUD$52 for osteoporosis, and AUD$85 for overactive bladder. (Table 1)

Sponsorship was highly concentrated by company. Figure 1 provides an overview of companies sponsoring ≥ 5% of events. All sell at least one drug for the relevant indication. Table 2 provides an overview of these drugs' PBS funding status. We present illustrative event descriptions featuring brand names in Table 3, with added details on sponsored events per company in on-line appendix Table 3.

Depression-related events

Two companies sponsored > 80% of depression-related events: Servier (51.2% of events), which markets the antidepressant agomelatine (Valdoxan) and AstraZeneca (23.0% of events), which markets quetiapine (Seroquel XR), an antipsychotic approved for depression treatment in patients intolerant to other therapies or with inadequate response. Neither agomelatine nor the depression indication for quetiapine are PBS-subsidised. Pfizer, which markets five PBS-subsidised antidepressants (desvenlafaxine, venlafaxine, sertraline, reboxetine, doxepin), was the next most frequent sponsor (16.0% of events).

We examined agomelatine and quetiapine sales volumes over the study period. Agomelatine sales tripled, from 99,625 units in 2012 to 300,103 units in 2015 (28 days treatment/unit). Sales of Seroquel XR (AstraZeneca), the quetiapine formulation approved for depression, increased from 247,374 units in 2012 to 374,917 in 2015 (60 days treatment/unit). Sales of other AstraZeneca quetiapine formulations decreased over the same period, from 499,445 units sold in 2012 to 202,783 in 2015. (19) (on-line Appendix, Figure 3.1)

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Seventy-nine AstraZeneca events focused on 'the anxious depressed patient'. Figure 2 is an invitation for one of these events, featuring the same image that was used in a Seroquel XR (quetiapine) advertisement that appeared in the *Medical Journal of Australia*. This formulation of quetiapine is also indicated for generalised anxiety disorder.

Osteoporosis-related events

Osteoporosis event sponsorship, similarly, was highly concentrated: Amgen and GSK, which co-market denosumab (Prolia), sponsored 31.3% and 18.1% of events respectively (in total, 49.4%). Novartis, which markets zoledronic acid (Aclasta) and oestradiol/norethisterone (Estalis continuous), a hormone therapy approved for osteoporosis prevention in high-risk women intolerant of other products, sponsored 19.9% of events; Servier, which markets strontium (Protos), sponsored 15.0%; and Sanofi, which marketed risedronic acid (Actonel) until December 2014, sponsored 8.7%. Denosumab, zoledronic acid, oestradiol/norethisterone, and risedronic acid are PBS-subsidised; strontium was delisted in August 2016 due to cardiac risks.

Sanofi transferred its marketing rights for risedronate to Actavis in December 2014. (20) Sanofi sponsored no osteoporosis events from October 2014 onwards. (Appendix Figure 1)

Denosumab dispensations increased nearly 7-fold over the study period, from 45,220 in 2012 to 309,350 in 2015. (21) Risedronate, zoledronic acid and strontium dispensations all decreased (on-line appendix, Figure 3.2) Of 193 events mentioning denosumab's brand name, Prolia, 104 were sponsored by Amgen and 88 by GSK.

Overactive bladder-related events

Two companies dominated sponsorship of overactive bladder events: Astellas (40.5% of events), which markets mirabegron (Betmiga) and solifenacin (Vesicare), the latter after October 2014, and CSL (40.0% of events), which marketed solifenacin from February 2011 to October 2014. Neither drug is PBS-subsidised. Astellas did not request PBS reimbursement for mirabegron. PBAC rejected solifenacin in 2007, judging benefits and cost-effectiveness to be uncertain.

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All CSL-sponsored overactive bladder events occurred while the company held distribution rights for solifenacin, e.g. to October 2014; most Astellas-sponsored events were held from 2014 onwards, when it obtained marketing rights. (on-line appendix Figure 2) Both solifenacin and mirabegron sales increased over the study period. (on-line appendix, Figure 3.3)

Discussion

In this analysis of 3,132 Australian pharmaceutical industry-sponsored events with 96,660 attendances, focusing on three clinical conditions prone to overdiagnosis, we found a strong concentration of sponsorship among few companies. Two companies sponsored over 70% of depression events; another two companies over 80% of overactive bladder events. In osteoporosis, the two companies that co-market denosumab sponsored nearly 50% of events.

Several products marketed by key event sponsors were considered unacceptable for PBS reimbursement, and are associated with cost, efficacy and safety concerns that have been flagged internationally. Servier, which sponsored over half of depression-related events, sells agomelatine, which is not PBS-subsidised. Agomelatine is not approved in the U.S. or Canada. A French independent drug bulletin, *Prescrire*, characterized the drug as "more dangerous than useful" and called for its withdrawal in 2015. (22) A Spanish bulletin, similarly, considered it, "worse than first-line antidepressants, up to 15-fold more expensive, and a worrying hepatic safety profile."(23)

A 2012 Cochrane systematic review found that AstraZeneca's atypical antipsychotic, quetiapine (Seroquel XR), had limited efficacy evidence for depression. (24) An updated systematic review, published in 2015, concluded that quetiapine had not been shown to improve function and that methodological biases had exaggerated benefits and minimised harm. (25)

Like agomelatine, denosumab (Prolia) is on the French bulletin *Prescrire*'s list of 71 drugs to avoid in 2016 because of "a disproportionate risk of adverse events" including serious infections due to immunosuppression, with only modest efficacy. (26) In 2015, half of all new Australian osteoporosis prescriptions were for denosumab. (27)

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All anticholinergic overactive bladder drugs, including solifenacin, have modest benefits, preventing one incontinence episode on average every two days, with frequent dry mouth and constipation, and there is observational evidence of dementia risk with longer-term use. (28) Mirabegron has similar efficacy to anticholinergics (28) and can lead to severe hypertension. (29)

This analysis is limited by the data available. Our analysis only includes 2.7% of events, a likely underestimate as not all event descriptions mention a condition. These three conditions are illustrative case studies and cannot be assumed to represent all condition-related sponsored events. However, a strength of this analysis is that it covers all sponsored events in Australia over four years, and coding was blinded to sponsor identity, types of attendees, gifts and costs. Due to the unique Australian dataset, this is the first such data-driven national analysis to examine condition-specific event sponsorship.

Company reports on financing of sponsored events provided limited information on content, leaving many questions unanswered. More research is needed on the messages in sponsored education, including on thresholds for disease diagnosis and treatment. Additionally, as individuals were not named, we could not directly evaluate the link between event attendance and individual prescribing patterns.

We could only examine potential contributions to overdiagnosis indirectly. We had hypothesized that events would focus on primary care, reflecting milder disease states. Nearly two-thirds of events, 62%, for the three conditions were attended by primary care doctors, versus 21% of other events. The focus on primary care was most pronounced for depression events: 74%.

The concentration of sponsorship by companies marketing products subject to safety, cost and efficacy concerns raises questions about influences on prescribing choice. This pattern is consistent with Brody and Light's hypothesis of an "inverse benefit law", in which intense marketing of drugs that may benefit a small proportion of patients is harmful to public health because a broader patient population is targeted than is likely to benefit. (30)

Many of these condition-focused events included dinner and were held in non-clinical settings such as restaurants. Costs per person were higher than for events in general. Even small gifts,

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such as food and drink, can affect behaviour. (31) An analysis of U.S. transparency reports found that physicians who receive ≥ 1 sponsored meal with a mean value of < US $20 were more likely to prescribe the promoted product, with larger effects observed the more meals received. (32)

Timing of sponsorship was linked to when a company sold a drug to treat the included condition, consistent with a sales orientation. Companies discontinued event sponsorship of overactive bladder and osteoporosis events when they no longer had marketing rights for a product for these conditions. This promotional orientation is consistent with internal documents released during the U.S. legal case on gabapentin, which described the use of CME to market off-label use. (33)

In this 4-year overview of industry-sponsored events focusing on depression, osteoporosis and overactive bladder, we found concentrated sponsorship among few companies per condition. These companies mainly market products that are not considered cost-effective choices for the specified conditions. This raises concerns about impacts on prescribing quality and on national prescribing trends. There was a strong focus on primary care physicians, frequent provision of dinner, and non-clinical setting. Promotion in primary care is consistent with a focus on a broader rather than narrower patient population. This observed pattern of event sponsorship raises concerns about the role of industry-sponsored education in conditions identified as prone to overdiagnosis, and highlights the need for continuing professional education to be free of commercial sponsorship.

Figure legends:

Figure 1:Percent of events sponsored by each company, in total and per condition*

Figure 2: Invitation for an AstraZeneca sponsored event

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Data sharing: The data set used for this study is publicly available at: http://dx.doi.org/10.4227/11/592631edbd9d5

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Access to the data: All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Previous presentations: Preliminary study results were presented at the *Preventing Overdiagnosis* conference in Barcelona, Spain, September 2016.

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References

1. Moynihan R. Doctors' education: the invisible influence of drug company sponsorship. BMJ. 2008;336(7641):416-7.

2. Marlow B. Is continuing medical education a drug-promotion tool?: NO. Canadian Family Physician. 2007;53(10):1650-2, 4-6.

3. Meixel A, Yanchar E, Fugh-Berman A. Hypoactive sexual desire disorder: inventing a disease to sell low libido. J Med Ethics. 2015;41(10):859-62.

4. Fauber J, Jones C, Fiore K. Slippery Slope: Testosterone Muscles Its Way to Profits. Medpage Today. October 18, 2015. Available at: http://www.medpagetoday.com/special-reports/slipperyslope/54156 Accessed January 17, 2017.

5. Spithoff S. Industry involvement in continuing medical education: time to say no. Canadian Family Physician. 2014;60(8):694-6, 700-3.

6. Hoffman JR, Cooper, R.J. Overdiagnosis of disease: a modern epidemic. Arch Intern Med. 2012;172(15):1123-4.

7. Moynihan R, Heath I, Henry D. Selling sickness: the pharmaceutical industry and disease mongering. BMJ.2002;324(7342):886-91.

8. Monk D. Improving transparency in the pharmaceutical industry. Australian Prescriber. 2016;39(4):110-111.

9. Dowrick C, Frances A. Medicalising unhappiness: new classification of depression risks more patients being put on drug treatment from which they will not benefit. BMJ. 2013;347.

10. Jarvinen TL, Michaelsson K, Jokihaara J, et al. Overdiagnosis of bone fragility in the quest to prevent hip fracture. BMJ. 2015;350:h2088.

11. Tikkinen KA, Auvinen A. Does the imprecise definition of overactive bladder serve commercial rather than patient interests? Eur Urol. 2012;61(4):746-8.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

12. Fabbri A, Grundy, Q, Mintzes B, et al. Pharmaceutical industry-funded events for health professionals: An analysis of data released under Australian transparency rules. BMJ Open 2017;7:e016701. doi:10.1136/ bmjopen-2017-016701

13. Australian Medicines Handbook. Adelaide, Australia: AMH; 2016.

14. Jerant A, Kravitz RL, Fernandez YGE, et al. Potential antidepressant overtreatment associated with office use of brief depression symptom measures. J Am Board Fam Med. 2014;27(5):611-20.

15. Mitchell AJ VA, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. Lancet. 2009;374:609–19.

16. Wong J MA, Eguale T, Buckeridge DL, Abrahamowicz M, Tamblyn R. Treatment Indications for Antidepressants Prescribed in Primary Care in Quebec, Canada, 2006-2015. JAMA 2016; 315(20):2230-1.

17. Organisation for Economic Cooperation and Development (OECD). Health at a Glance 2015: How does Australia compare? Available at: https://www.oecd.org/australia/Health-at-a-Glance-2015-Key-Findings-AUSTRALIA.pdf Accessed January 16, 2017.

18. Elliott C. White Coat, Black Hat. Adventures on the Dark Side of Medicine. Boston, MA, USA: Beacon Press; 2010.

19. QuintilesIMS. Quetiapine Fumarate unit sales in Australia, 2012 to 2015. *Data provided to authors on request by QuintilesIMS, November 2016.*

20. Actavis takes back Actonel December 12, 2014. Available at: https://pharmadispatch.com/news/actavis-takes-back-actonel Accessed January 9, 2017.

21. Pharmaceutical Benefits Scheme. Australian Department of Health. ASM_Table_1. Australian Statistics on Medicine. 2012 to 2015. Available at: https://www.pbs.gov.au/info/browse/statistics - Expenditure2016 Accessed January 25, 2017.

For peer review only

22. Prescrire Editorial Staff. Pour mieux soigner, des médicaments à écarter : bilan 2015. La Revue Prescrire. 2015;35(376):144-51.

23. Anonymous. Agomelatine (Valdoxan). Worse than first-line antidepressants, up to 15-fold more expensive, and a worrying hepatic safety profile. Drug Assessment Report Drug and Therapeutics Bulletin of Navarre. DAR no. 3. 2010. Available at: http://www.navarra.es/home_en/Temas/Portal+de+la+Salud/Profesionales/Documentacion+y+publicaciones/Publicaciones+tematicas/Medicamento/FET/2010/DAR+No+3+Agomelatine.htm Accessed January 25, 2017.

24. Komossa K, Depping, AM, Gaudchau A et al. Second-generation antipsychotics for major depressive disorder and dysthymia. . Cochrane Database of Systematic Reviews. 2010;12.

25. Therapeutics Initiative. Antipsychotics should not be used for non-psychotic depression. Therapeutics Letter 95. September 30, 2015. Available at: http://www.ti.ubc.ca/2015/09/30/antipsychotics-should-not-be-used-for-non-psychotic-depression/ Accessed January 16, 2017.

26. Prescrire Editorial Staff. Towards better patient care: drugs to avoid in 2016. Prescrire International. 2016;25(170):105-11.

27. McColl G. Chair, Drug Utilisation Sub Committee. Drug Utilisation Committee Outcome Statement 29-30 September 2016. Canberra, Australia. Pharmaceutical Benefits Advisory Committee, Pharmaceutical Benefits Service. 2016. Available at: http://www.pbs.gov.au/industry/listing/elements/dusc-meetings/dos/dusc-dos-sep-2016.pdf Accessed January 16, 2017.

28. Therapeutics Initiative. Are claims for newer overactive bladder drugs warranted? Therapeutics Letter 93, April 22, 2015. Available at: http://www.ti.ubc.ca/2015/04/22/are-claims-for-newer-drugs-for-overactive-bladder-warranted/ Accessed January 26, 2017.

29. Medicines and Health Products Regulatory Agency, UK. Mirabegron (Betmiga▼): risk of severe hypertension and associated cerebrovascular and cardiac events. Drug Safety Update. 14 October, 2015. Available at: https://www.gov.uk/drug-safety-update/mirabegron-betmiga-

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risk-of-severe-hypertension-and-associated-cerebrovascular-and-cardiac-events Accessed January 20, 2017.

30. Brody H, Light DW. The Inverse Benefit Law: How Drug Marketing Undermines Patient Safety and Public Health. American Journal of Public Health. 2011;101(3):399-404.

31. Dana J, Loewenstein G. A Social Science Perspective on Gifts to Physicians From Industry. JAMA. 2003;290(2):252-5.

32. DeJong C, Aguilar T, Tseng C, Lin GA, Boscardin W, Dudley R. Pharmaceutical industry–sponsored meals and physician prescribing patterns for medicare beneficiaries. JAMA Internal Medicine. 2016;176(8):1114-10.

33. Steinman MA, Bero LA, Chren M, Landefeld C. Narrative review: The promotion of gabapentin: an analysis of internal industry documents. Ann Intern Med. 2006;145(4):284-93.

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34.

Table 1: Characteristics of sponsored events for the three conditions

	Total events n=116,845	Depression n=1,567	Osteoporosis n=1,375	Overactive bladder n=190
Attendees				
Total number of attendees (% of total)	3,481,750	41,472 (1.2%)	33,916 (1.0%)	21,270 (0.6%)
Median/ event (IQR)	18 (12-25)	19 (12-28)	19 (12-27)	20 (13-34)
Clinicians present (% of events)				
Medical specialists	80,060 (68.5%)	839 (53.5%)	921 (67.0%)	50 (26.3%)
Primary care doctors	24,662 (21.1%)	1,159 (74.0%)	638 (46.4%)	132 (69.5%)
Trainees	44,774 (38.3%)	222 (14.2%)	531 (38.6%)	18 (9.5%)
Nurses	46,214 (39.6%)	357 (22.8%)	359 (26.1%)	46 (24.2%)
Types of medical specialists present (% of events)				
Most frequent	Oncology 19,723 (16.9%)	Psychiatry 804 (51.3%)	Endocrinology 516 (37.5%)	Urology 30 (15.9%)
Second	Surgery 10,670 (9.1%)	Geriatrics 55 (3.5%)	Rheumatology 190 (13.8%)	Ob/Gyn 13 (6.8%)
Expenses (AUD$)				
Total cost of events	$286,117,928	$6,259,581(2.2%)	$6,073,333(2.1%)	$568,332 (0.2%)
Median cost per event (IQR)	$263 ($153-1,195)	$1,941 ($659–3,264)	$686 ($217-2,500)	$2,012 ($765-3,370)
Median cost per head (IQR)	$14 ($10-68)	$104 ($48-141)	$52 ($13-119)	$85 ($31-90)
Food & drink cost (% of total cost)	$84,862,791 (30%)	$2,441,950 (39%)	$2,314,319 (38%)	$233,548 (41%)
Median per event food & drug cost (IQR)	$197 ($107-405)	$911 ($135– 1,712)	$337 ($150 - 1,478)	$1,115 ($91-1868)
Median per head food & drink cost (IQR)	$12 ($8-20)	$57 ($11-77)	$17 ($11-75)	$55 ($11-80)
Event characteristics				
Clinical setting	74,998 (64.2%)	487 (31.1%)	692 (50.3%)	44 (23.2%)
Any food provided	105,667(90.4%)	1441 (92.0%)	1298 (94.4%)	158 (83.2%)
Dinner	19,873 (17.0%)	811 (51.7%)	512 (37.2%)	41 (21.6%)
Lunch	25,935 (22.2%)	241 (15.4%)	485 (35.3%)	28 (14.7%)
Tea	14,067 (12.0%)	15 (1.0%)	69 (5.0%)	2 (1.1%)
Breakfast	12,806 (11.0%)	24 (1.5%)	77 (5.6%)	7 (3.7%)
All-day event meals	3,113 (2.7%)	62 (4.0%)	58 (4.2%)	1 (0.5%)
Unspecified	29,873 (25.6%)	288 (18.4%)	97 (7.1%)	79 (41.6%)

Abbreviations: IQR = interquartile range

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Table 2: Pharmaceutical Benefits Scheme (PBS) subsidy of drugs marketed for depression, osteoporosis, and overactive bladder marketed by sponsoring companies

Company	Drug for condition (brand)	PBS subsidy?(Y/N)	PBAC decisions and rationale for restrictions	Notes
Depression				
Servier	Agomelatine (Valdoxan)	No	Nov 2010: uncertainty; inappropriate comparator July 2011, March 2012: superior clinical effectiveness and safety over SSRIs not demonstrated	
AstraZeneca	Quetiapine (Seroquel XR)[a]	No for MDD, treatment-resistant depression or anxiety disorders.	Nov 2011: inadequate clinical evidence to support superiority. July 2013: non-inferior comparative safety and effectiveness not established	Quetiapine is PBS-funded for schizophrenia; acute mania & bipolar disorder
Pfizer	Desvenlafaxine (Pristiq)	Yes	Nov 2008: *cost minimisation*[b] vs. venlafaxine; no evidence of therapeutic advantage.	
	Venlafaxine (Efexor-XR, Altven),Sertraline (Zoloft),Reboxetine (Edronax),Doxepin (Sinequan)	Yes	*General schedule*[c] listings, major depressive disorder.	
Osteoporosis				
Amgen and GSK	Denosumab (Prolia)	Yes	July 2010: *cost-minimisation*[b] vs. zoledronic acid Nov 2011: *Streamlined Authority*[d] , post-menopausal osteoporosis, age 70+, BMD T-score ≤ -2.5; cost-minimisation vs. alendronate July 2013: superiority vs. zoledronic acid rejected; non-inferiority accepted	2009: co-commercialised by Amgen and GSK; Dec 2015: Amgen reacquires all marketing rights in Australia.
Novartis	Zoledronic acid (Aclasta)	Yes	July 2008: *Authority Required* [e] cost-minimisation vs. alendronate; Nov 2008: listing extended: women aged 70+; BMD T-score ≤-3.0 Nov 2009: extended to men July 2011: 3-year limit removed; listing changed to *Streamlined Authority*	
	Oestradiol/ norethisterone (Estalis continuous)	Yes	*General Schedule*[c]	

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Company	Drug for condition (brand)	PBS subsidy?(Y/N)	PBAC decisions and rationale for restrictions	Notes
Servier	Strontium (Protos)	No (previously subsidised)	July 2015: restricted to severe established osteoporosis, patients unable to use other drugs, without cardiovascular contraindications Aug 2016: delisted due to cardiac risks	
Sanofi	Risedronic acid (Actonel, Actonel Ec, Actonel Ec Combi, Actonel Ec Combi D)	Yes	Feb 2001: postmenopausal osteoporosis; minimal fracture trauma; *cost-minimisation* vs. alendronate Dec 2001 - extended to corticosteroid-induced osteoporosis March 2013: extended to patients aged 70 + BMD T-score ≤ -2.5	Dec 2014: Sanofi transfers marketing rights to Actavis
Overactive bladder				
Astellas	Mirabegron (Betmiga)	No	N/A. No request made for PBS listing	
CSL and Astellas	Solifenacin (Vesicare)	No	July 2007: uncertain clinical benefit and cost-effectiveness	Feb 2011 – Oct 2014: marketed by CSL Oct 2014: Astellas regains marketing rights

a. Immediate release quetiapine products are not indicated for major depressive disorder (MDD) or general anxiety disorder, only Seroquel XR.
b. *Cost-minimisation*: product is considered non-inferior in safety and efficacy to listed comparator; no higher pricing allowed.
c. *General Schedule:* no prior authority required.
d. *Streamlined Authority*: no prior approval required, but a streamlined authority code is required on the prescription; if quantities and/or repeats exceed specified levels, treated as *Authority Required*.
e. *Authority Required*: telephone or written approval required from Department of Health prior to prescribing.

Abbreviations: BMD = bone mineral density; GSK= GlaxoSmithKline; MDD = major depressive disorder; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme

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Table 3: Illustrative examples of verbatim descriptions of sponsored events

Sponsor	Date	Event content	Venue	Professionals Present	Hospitality	Total Cost
Servier	05/12	120 minute presentation including a discussion on Valdoxan specific patient cases	The Sebel Resort, Windsor, NSW	26 Advanced Trainees, Hospital Pharmacists, Psychiatrists	Dinner, including alcoholic and non-alcoholic beverages	$4138.84
Astrazeneca	08/14	Educational dinner meeting for General Practitioners with a specialist presentation on The Anxious Depressed Patient. 1 hour educational content	Kimberly Gardens St Kilda East VIC	35 GPs, Psychiatrists	Dinner with alcoholic and non alcoholic beverages	$3,750.00
GSK	06/15	HCP Osteoporosis presentation. Providing HCPs with the confidence to switch appropriate patients from bis-phosphonates to Prolia. GSK was not responsible for organising the educational content. Duration of Educational Content: 2 hour	GG Restaurant, 105 Yarra St, Geelong VIC 3220	38 GPs, Endocrinologists	Three Course Dinner, Juice / Water, Non Alcoholic Beverage, Alcoholic Beverage	$4,136.5
Astellas	04/14	Educational Dinner Meeting. Prof Philip Van Kerrebroeck giving educational launch presentation on BETMIGA, the new oral treatment in the management of Over Active Bladder. One hour educational content.	The Terrace Room (Private Dining), L'Aqua, Sydney, NSW	10 leading specialists with an interest in OAB - especially Urologists	Food & Beverages	$11,742.95

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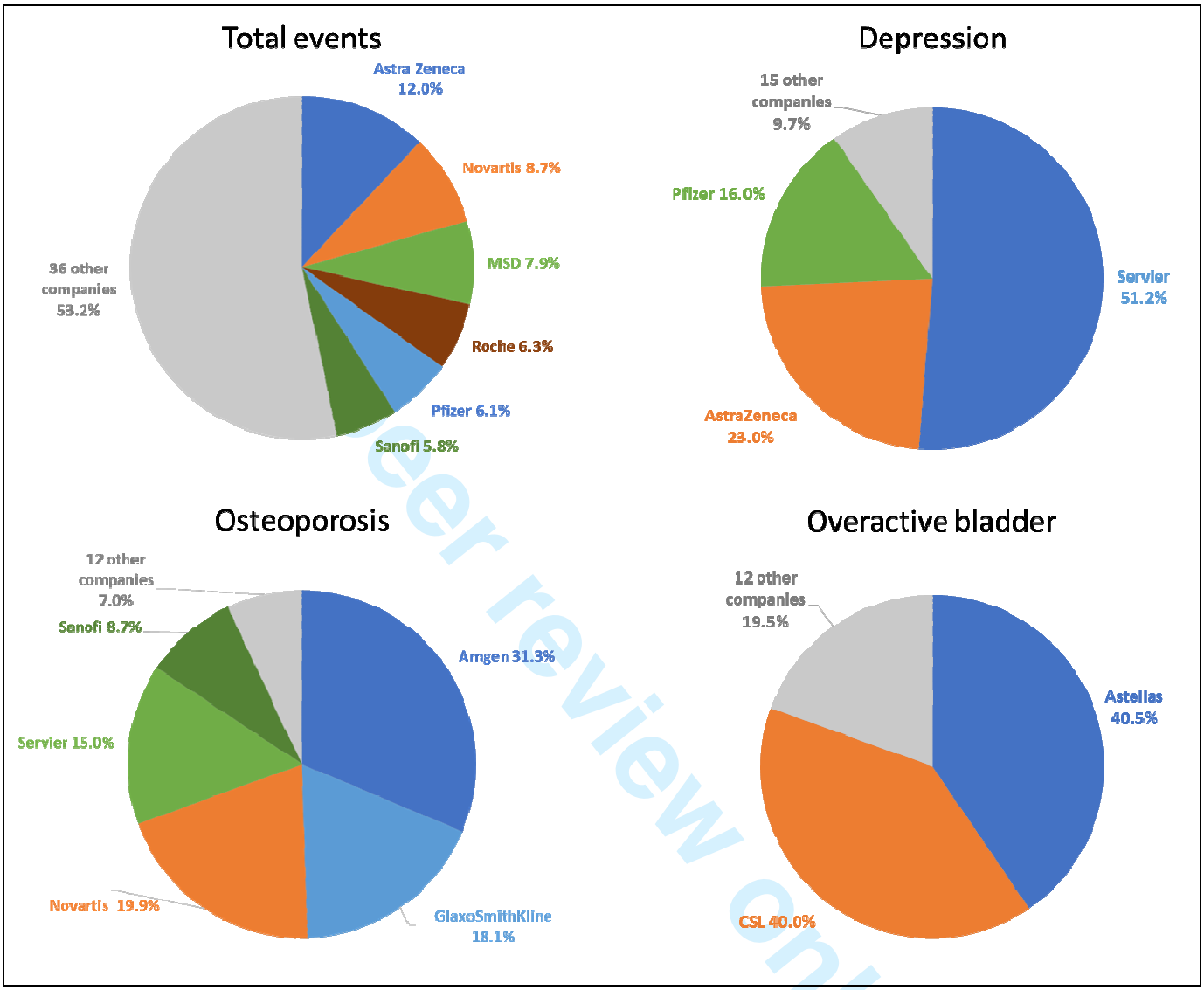
Figure 1:Percent of events sponsored by each company, in total and per condition*



* All companies sponsoring ≥ 5% of events are listed.

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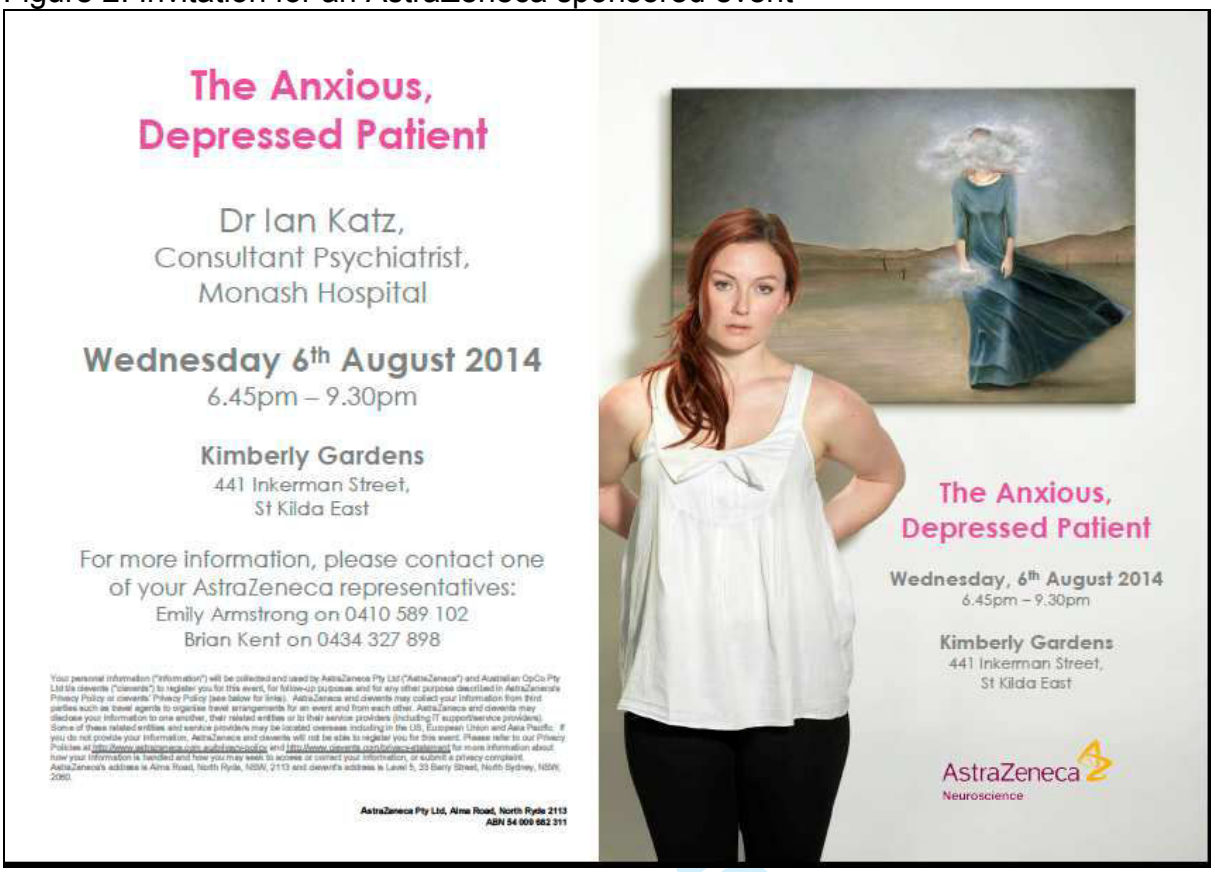
Figure 2: Invitation for an AstraZeneca sponsored event



Available at : http://ajmf.org.au/wp-content/uploads/2014/07/AJMF-VIC-Aug-2014-meeting-Kimberly-Gardens2.pdf. Accessed January 27, 2016. An advertisement with the same image ran in the May 20, 2013 issue of the *Medical Journal of Australia*.

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On-line Appendix:

Mintzes et al. How does industry-sponsored education market overdiagnosed conditions? A cohort study of depression, osteoporosis and overactive bladder events in Australia

Appendix Table 1:
Coding of event characteristic and audience variables

Variable name	Keyword search
COMPANY	A. Menarini Australia Pty Ltd; Abbott Australasia Pty Ltd OR AbbVie Pty Ltd; Actelion Pharmaceuticals Australia Pty Ltd; Alexion Pharmaceuticals Australasia PTY LTD; Allergan Australia Pty Ltd; Amgen Australia; Astellas Pharma Australia Pty Ltd; Astrazeneca Pty Ltd; Baxter Healthcare Pty Ltd; Bayer Australia Ltd; Besins Healthcare Australia; BioCeuticals; Biogen Idec Australia Pty Limited; Boehringer Ingelheim Pty Limited; Bristol-Myers Squibb Australia Pty Limited; Celgene Pty Ltd; CSL (includes also bioCSL Australia Pty Ltd and CSL Behring); Eisai Australia Pty Ltd; Eli Lilly Australia Pty Ltd; Fresenius Kabi Australia; Gilead Sciences Pty.; GlaxoSmithKline Australia Pty Ltd *+ (GSK); iNova Pharmaceuticals (Aus) Pty Ltd; IPSEN Pty Ltd; Janssen; LEO Pharma Pty Ltd; Lundbeck Australia; Merck Serono Australia Pty Ltd; MSD Australia Pty Ltd; Mundipharma Pty Ltd; Mylan EPD; Norgine Pty Limited; Novartis Pharmaceuticals Australia Pty Limited (includes also Alcon Laboratories); Novo Nordisk Pharmaceuticals; Pfizer Australia; Roche Products Pty Limited; Sanofi/Sanofi Aventis Australia Pty Ltd; Servier Laboratories (Australia) Pty Ltd; Shire Australia; Takeda Pharmaceuticals Australia Pty Ltd (includes also Nycomed Pty Ltd Report); UCB Pharma; Vifor Pharma Pty Ltd
LOCATION	
New South Wales	NSW, New South Wales, Sydney, other cities or suburbs, and postal codes of NSW*
Victoria	VIC, Victoria, Melbourne, other cities or suburbs and postal codes of VIC*
Australian Capital Territory	ACT, Australian Capital Territory, Canberra, other cities or suburbs, and postal codes of ACT*
Western Australia	WA, Western Australia, Perth, other cities or suburbs, and postal codes of WA*

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Variable name	Keyword search
South Australia	SA, South Australia, Adelaide, other cities or suburbs, and postal codes of SA*
Northern Territory	NT, North Territory, other cities or suburbs, and postal codes of NT*
Tasmania	TAS, Tasmania, Hobart, other cities or suburbs, and postal codes of Tasmania*
Overseas	Overseas: outside of Australia**
*Where the state or capital was not listed, events were hand coded based on postal codes, cities or suburbs **Events not taking place in an Australian state were hand-coded	
MEALS	
• Lunch	Lunch
• Dinner	Dinner
• Breakfast	Breakfast
• Tea	Afternoon tea, morning tea, light refreshments, light meals, sandwiches & drinks, coffee cart, snack and beverage, sushi
• All day events w/ meals	Day delegate package*; conference package**
• Food unspecified	food & beverages, meals, drinks, in hospital catering, beverages, wine
• No meals provided	Sponsorship/accommodation only, no hospitality provided, travel/accommodation only (domestic events)
*Note: “day delegate package” consisted of entries where multiple meals were listed ((Lunch, tea), (Breakfast, tea), (Dinner, tea), (Breakfast, lunch, tea)) **Note: “conference package” consisted of events lasting multiple days and typically included a day delegate package, often accommodation (food and beverage not reported separately), registration (food and beverage not reported separately), or travel (including flights, registration, airfares, accommodation and food and beverages not reported separately)	
EVENTS HELD IN CLINICAL SETTING	Hospital; clinic; practice; medicare local; health centre; surgery; medical centre; medical; health care centre; specialist centre; cancer centre; cancer care centre; heart centre; medical and dental centre; endocrine centre; radiotherapy centre; radiation centre; optical centre; eye centre; renal unit; ward; department; dept; community health; family planning; education centre.
PROFESSIONAL STATUS	
• Primary care doctors	GP; general practitioner; family medicine.

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Variable name	Keyword search
• Nurses	Nurse
• Pharmacists	Pharmacist
• Trainees	Registrar; resident; intern; student; advanced trainee; RMO; resident medical officer; JHO; SHO; senior house officer; PHO; principal house officer; fellow
• Specialty care	Specialist; consultant; senior medical officer; SMO; visiting medical officer; VMO; general medicine; general physician; *ology physician; *ology doctor; allergist; allergy physician; anesthesiologist; anesthetist; anaesthesiologist; anaesthetist; andrologist; cardiologist; dermatologist, diabetologist; emergency physician; emergency medicine physician; endocrinologist; epileptologist; gastroenterologist; geriatrician; getriatric physician; gynaecologist; obstetrician; OB/GYN; haematologist; hematologist; hepatologist; immunologist; infectious disease physician; infectious disease doctor; internal medicine physician; microbiologist; neonatologist; neurologist; nuclear medicine physician; nephrologist; renal physician; renal doctor; urologist; oncologist; pharmacologist; pulmonologist; psychogeriatrician; ophthalmologist; rheumatologist; radiologist; respiratory physician; respiratory medicine physician; respiratory medicine doctor; palliative care physician; pathologist; sexual health physician; sexual health doctor; psychiatrist; psychiatry doctor; paediatrician; surgeon; surgery doctor; intensive care doctor; intensivist; intensive care physician; cardiothoracic
CLINICAL FOCUS	
• Allergy/Immunology	Allergist; allergy; immunologist; immunology
• Anaesthesiology	Anesthesiologist; anesthetist; anaesthesiologist; anaesthetist; anaesthesiology
• Andrology	Andrologist
• Cardiology	Cardiologist; cardiology
• Dermatology	Dermatologist; dermatology
• Emergency	Emergency
• Endocrinology	endocrinologist; endocrinology; diabetologist; diabetology; diabetes
• Gastroenterology	Gastroenterologist; gastroenterology; Hepatologist; hepatology
• Geriatrics	Geriatrician; geriatric; psychogeriatrician; elderly
• Haematology	Haematologist; haematology; hematology; hematologist

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Variable name	Keyword search
• Infectious Diseases	Infectious disease; microbiologist; microbiology
• Internal Medicine	Internal medicine
• Intensive care	Intensive care; intensivist; critical care
• Neonatology	Neonatologist; neonatology; NICU; neonatal
• Nuclear medicine	Nuclear medicine
• Nephrology	Nephrologist, nephrology; renal; kidney
• Neurology	Neurologist; neurology; epileptologist
• Obstetrics/Gynaecology	Gynaecologist; gynaecology; obstetrician; OB/GYN; obstetrics
• Oncology	Oncologist; oncology; cancer
• Ophthalmology	Ophthalmologist; ophthalmology
• Otolaryngology	Otolaryngology
• Palliative care	Palliative care
• Pathology	Pathologist; pathology
• Pharmacology	Pharmacologist; pharmacology
• Paediatrics	Paediatrician; paediatric*; pediatric*
• Psychiatry	Psychiatrist; psychiatry; mental health
• Radiology	Radiologist; radiology
• Rheumatology	Rheumatologist; rheumatology
• Respiratory medicine	Lung specialist; respiratory; pulmonologist
• Sexual health	Sexual health
• Surgery	Surgeon; surgery; surgical; operating theatre
• Urology	Urologist; urology
*Note: clinical focus is a proxy variable based on clinical specialty of attendees and/or event description.	
EVENT TYPE	
• Meeting (not otherwise specified)	Search for generic word “meeting”
• Journal club	Journal club; journalclub
• Inservice	Inservice
• Workshop	Workshop
• Grand rounds	Grand round; grandround
• Scientific meeting	scientific meeting; congress; conference AND NOT videoconference/teleconference
• Clinical meeting	internal meeting; departmental meeting; clinical meeting; case review, case conference; case study meeting; case study conference
• Multidisciplinary meeting	Multidisciplinary meeting

Appendix Table 2:

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Coding of three included conditions

Variable name	Keyword search
DEPRESSION	Depress; Anx; Citalopram; Sertraline; Agomelatine; Vortioxetine; Amitriptyline; Clomipramine; Desvenlafaxine; Dothiepin; Doxepin; Duloxetine; Escitalopram; Fluoxetine; Fluvoxamine; Imipramine; Miaserin; Mirtazapine; Moclobemide; Paroxetine; Reboxetine; Tranylcypromine; Trimipramine; Venlafaxine; Brintellix; Valdoxan; Cymbalta; Anafranil; Pristiq; Sinequan; Andepra; Prozac; Tolvon; Avanza; Mirtazon; Remero; Edronax; Zoloft; Xydep; Altven; Efexor
OSTEOPOROSIS	osteop; bone health; bone disease; metabolic bone disease; mineral bone disease; bone mineral; mineral bone; bone and calcium; fracture; Bisphosphonate; Denosumab; Zolendronic acid; Cinacalcet; Teriparatide; Alendronic acid; Alendronate; Cholecalciferol; Calcitriol; Calcium chloride; Disodium Pamidronate; Ibandronate; Raloxifene; Risedronate ; Salcatonin; Sodium Clodronate; Strontium ranelate; Tiludronate; Prolia; Forteo; Sensipar; Adronat; Fosamax; Dronalen; Rocaltrol; Risedronate; Aredia; Bondronat; Evifyne; Evista; Miacalcic; Protos; Skelid; Aclasta; Osteovan; Zometa.
OVERACTIVE BLADDER	Incontinence; Overactive AND bladder; Over active AND bladder; Betmiga; Darifenacin; Oxybutynin; Propantheline; Solifenacin; Tolterodine; Mirabegron; Ditropan; Vesicare; Detrusitol

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Appendix Table 3:

Top 5 sponsoring companies in total and per condition

Company	Number of events (% of category)	Number of attendees (% of category)	Total cost of food and beverage ($AUD)	Total cost of functions ($AUD)	Mean total cost per event (SD) (AUD$)	Median total cost per event (IQR) (AUD$)
General	116,845	3,481,750	84,862,791	286,117,928	2,449.70 (SD=15,020)	263 (153-1,195)
AstraZeneca	13,968 (12.0%)	435,686 (12.5%)	12,725,027 .09 (15.0%)	31,766,776 (11.1%)	2,274 (SD=10,878)	318 (165-2,261)
Novartis	10,120 (8.7%)	244,069 (7.0%)	6,600,502. 76 (7.8%)	27,467,246 (9.6%)	2,714 (SD=16,109)	270 (167-1,154)
MSD	9,142 (7.8%)	214,621 (6.2%)	5,388,246. 54 (6.4%)	18,352,116 (6.4%)	2,007 (SD=9,274)	341 (180-1,182)
Roche	7,383 (6.3%)	174,878 (5.0%)	2,891,426. 00 (3.4%)	16,625,126 (5.8%)	2,252 (SD=22,101)	186 (129-284)
Pfizer	7,125 (6.1%)	188,439 (5.4%)	3,740,677. 35 (4.4%)	18,464,785 (6.5%)	2,591 (SD=21,482)	236 (141-573)
Depression	1,567	41,472	2,441,950	6,259,581	3,995 (SD=15,895)	1,941 (659 – 3,264)
Servier	803 (51.2%)	19,671 (47.4%)	1,497,510 (61.3%)	3,757,665 (60.0%)	4,680 (SD=1,7837)	2,164 (921 - 3,145)
AstraZeneca	361 (23.0%)	9,577 (23.1%)	551,985 (22.6%)	1,269,764 (20.3%)	3,517 (SD =5,306)	1,082 (126-2,045)
Pfizer	251 (16.0%)	5,160 (12.4%)	182,306 (7.5%)	326,255 (5.2%)	1,300 (SD=1,846)	420 (195-1,978)
Eli Lily	57 (3.6%)	1,175 (2.8%)	28,902 (1.2%)	47,485 (0.8%)	833 (SD=1,591)	165 (75-950)
Janssen	33 (2.1%)	974 (2.35%)	5,760 (0.24%)	56,953 (0.91%)	1,726 (SD=5,788)	187 (106-273)
Osteoporosis	1,375	33,916	2,314,319	6,073,333	4,417 (SD=21,611)	686 (217-2,500)
Amgen	431 (31.4%)	10,120 (29.84%)	943,254 (40.8%)	2,114,304 (34.8%)	4,906 (SD=29,502)	259 (175-630)
Novartis	274 (19.9%)	5,735 (16.91%)	308,064 (13.3%)	971,212 (16.0%)	3,545 (SD=16,701)	369 (159-2,011)
GSK	249 (18.1%)	5,273 (15.55%)	474,364 (20.5%)	928,803 (15.3%)	3,730 (SD=11,982)	2,354 (1,500-3,532)
Servier	206 (15.0%)	4,344 (12.81%)	283,954.11 (12.3%)	523,699.04 (8.6%)	2,542 (SD=6,636)	1,647 (546-2,939)

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Company	Number of events (% of category)	Number of attendees (% of category)	Total cost of food and beverage ($AUD)	Total cost of functions ($AUD)	Mean total cost per event (SD) (AUD$)	Median total cost per event (IQR) (AUD$)
Sanofi	119 (8.7%)	3,798 (11.20%)	100,970.91 (4.4%)	190,200.21 (3.1%)	1,598 (SD=3,205)	440 (120-1,755)
Overactive bladder	190	21,270	467,096	1,136,665	5,951 (SD=41,070)	2,024 (773-3,379)
Astellas	77 (40.5%)	2,294 (10.8%)	113,572 (24.3%)	209,663.47 (18.5%)	2,723 (SD=2,616)	2,277 (1,568-2,956)
CSL	76 (40.0%)	1,950 (9.2%)	94,902 (20.3%)	181,431 (16.0%)	2,387 (SD=2,399)	1,664.50 (169-3,579)
AstraZeneca	9 (4.7%)	194 (0.9%)	3,802 (0.8%)	11,911 (1.0%)	1,323 (SD=883)	795.07 (795-1,778)
Allergan	6 (3.2%)	681 (3.2%)	14,068 (3.0%)	54,569 (4.8%)	9,095 (SD=6,445)	10,654 (1,389-15,148)
Bristol-Myers Squibb	6 (3.2%)	2,710 (12.7%)	900 (0.2%)	66,400 (5.8%)	11,067 (SD=7,645)	16,000 (1,350-16,000)

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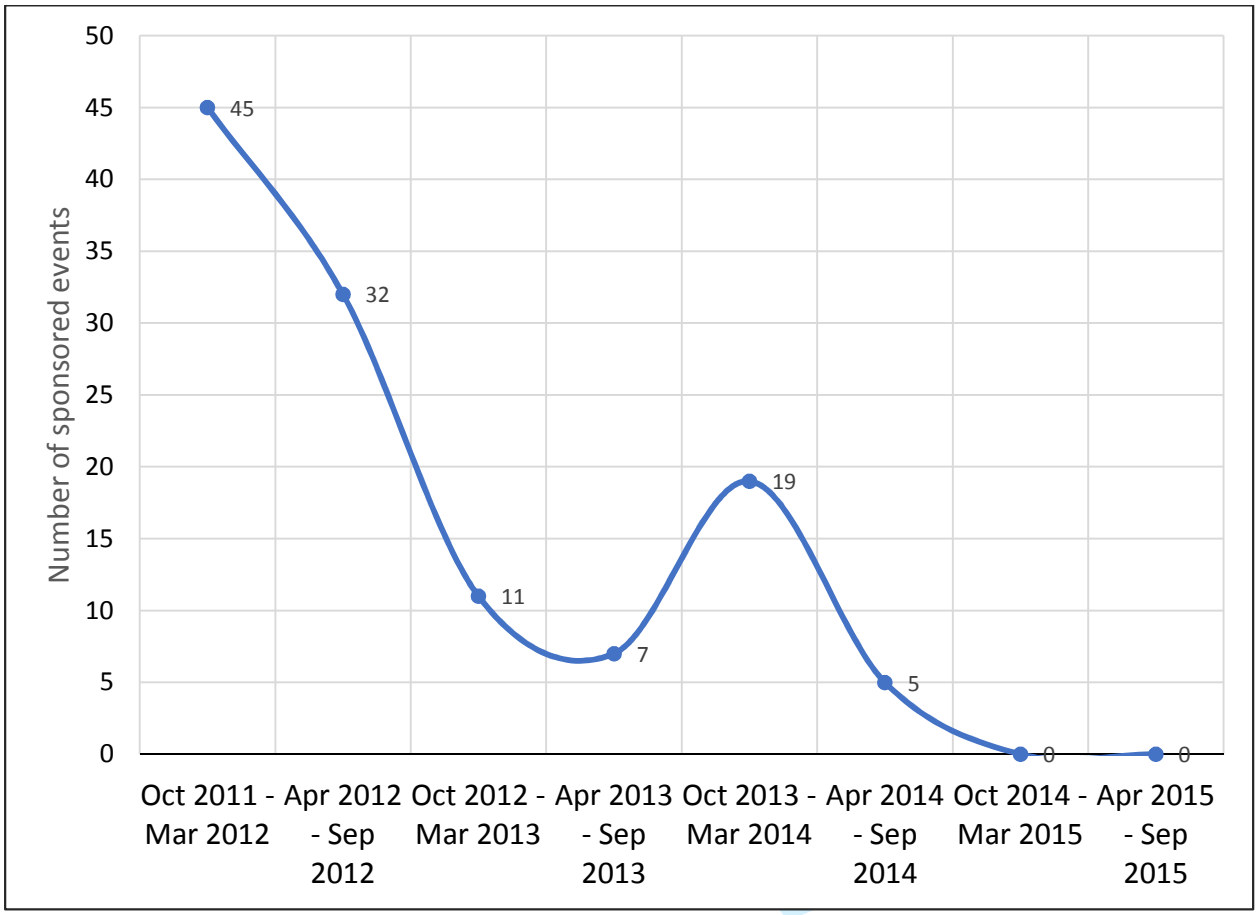
Appendix Figure 1:

Osteoporosis-related events sponsored by Sanofi



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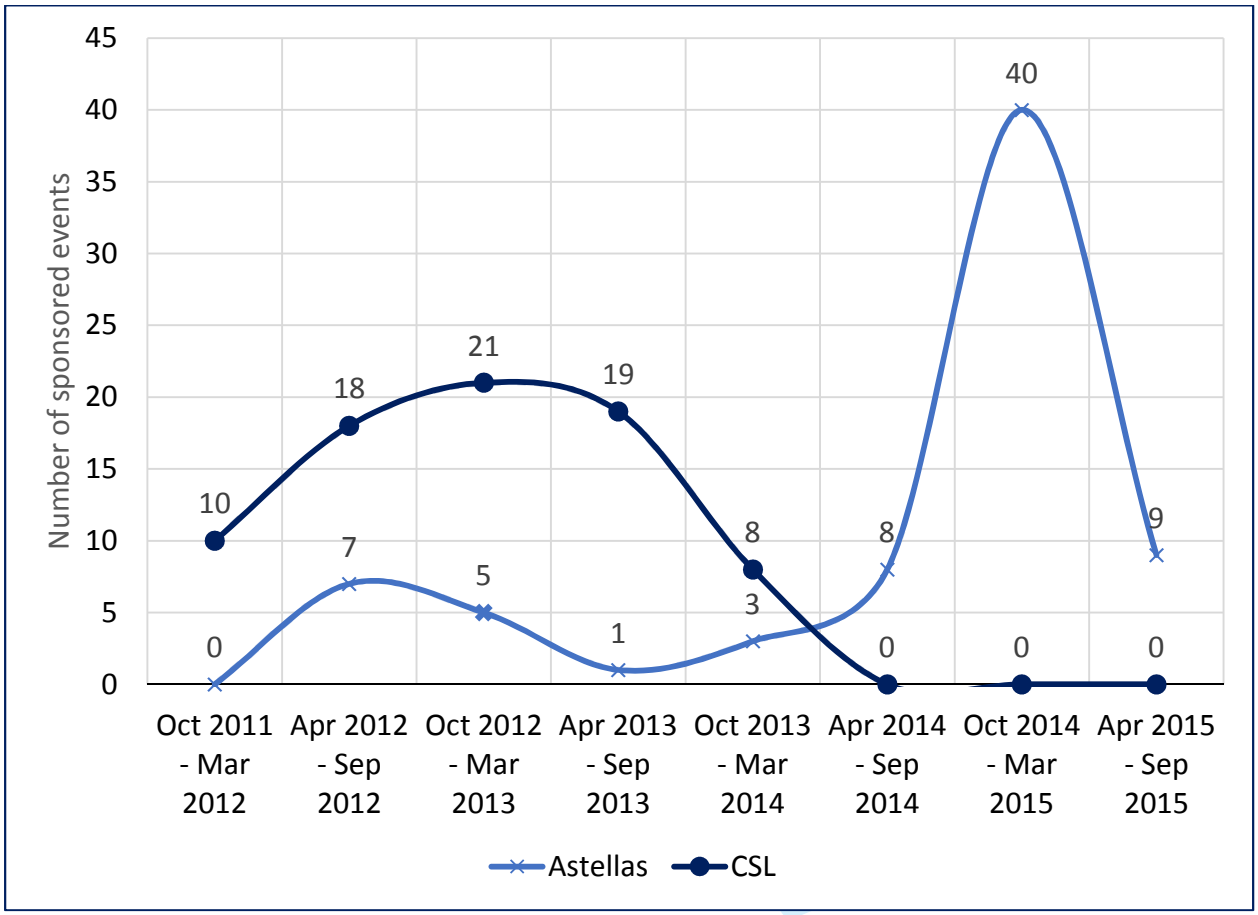
Appendix Figure 2:

Event sponsorship over the study period by lead overactive bladder sponsors



Note: CSL marketed solifenacin in Australia from February 2011 to October 2014, when marketing rights shifted to Astellas. Astellas also markets mirabegron, approved in Australia in February 2014.

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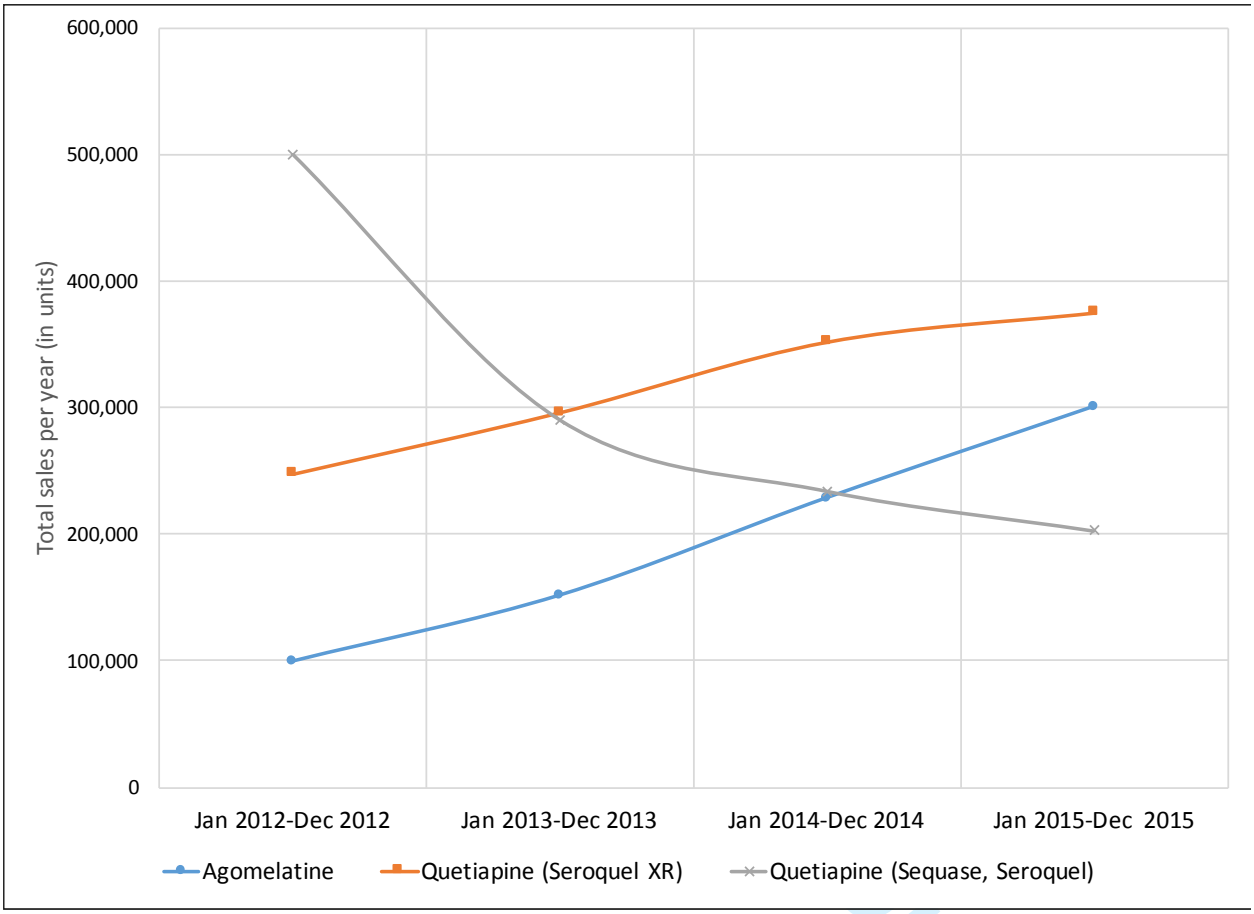
Appendix Figure 3: Product sales over the study period

Figure 3.1: Annual sales of agomelatine, quetiapine for depression (Seroquel XR) and other formulations of quetiapine (Sequase, Seroquel)



Agomelatine: 1 unit = 28 days@ 25mg/day; quetiapine (Seroquel XR, Sequase, Seroquel): 1 unit = 60 days (various doses) Source: IMS Quintiles

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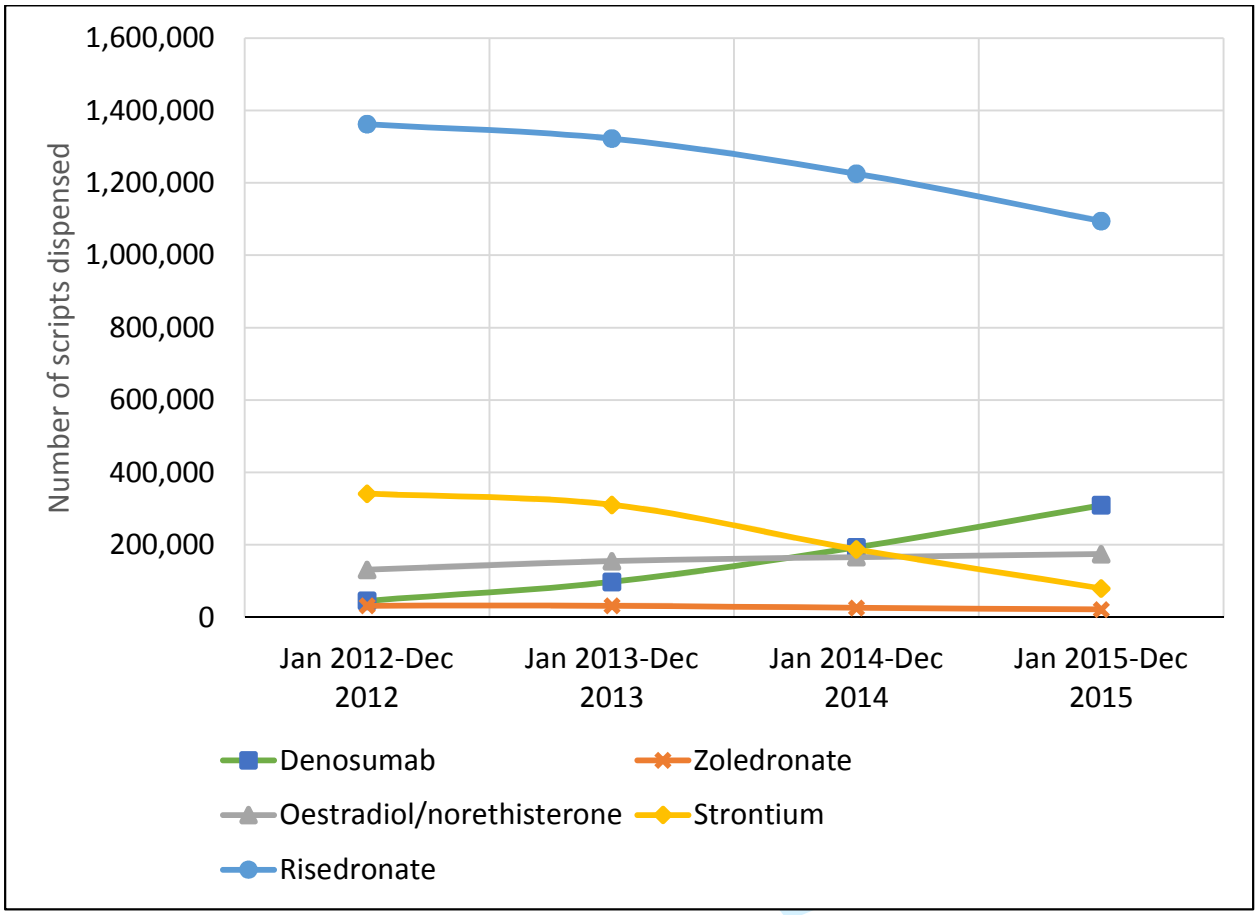
Appendix Figure 3.2

Number of scripts dispensed for osteoporosis drugs, Pharmaceutical Benefits Scheme (PBS)



Source: Australian Statistics on Medicines 2012 to 2015. Available at: https://www.pbs.gov.au/info/browse/statistics#ASM

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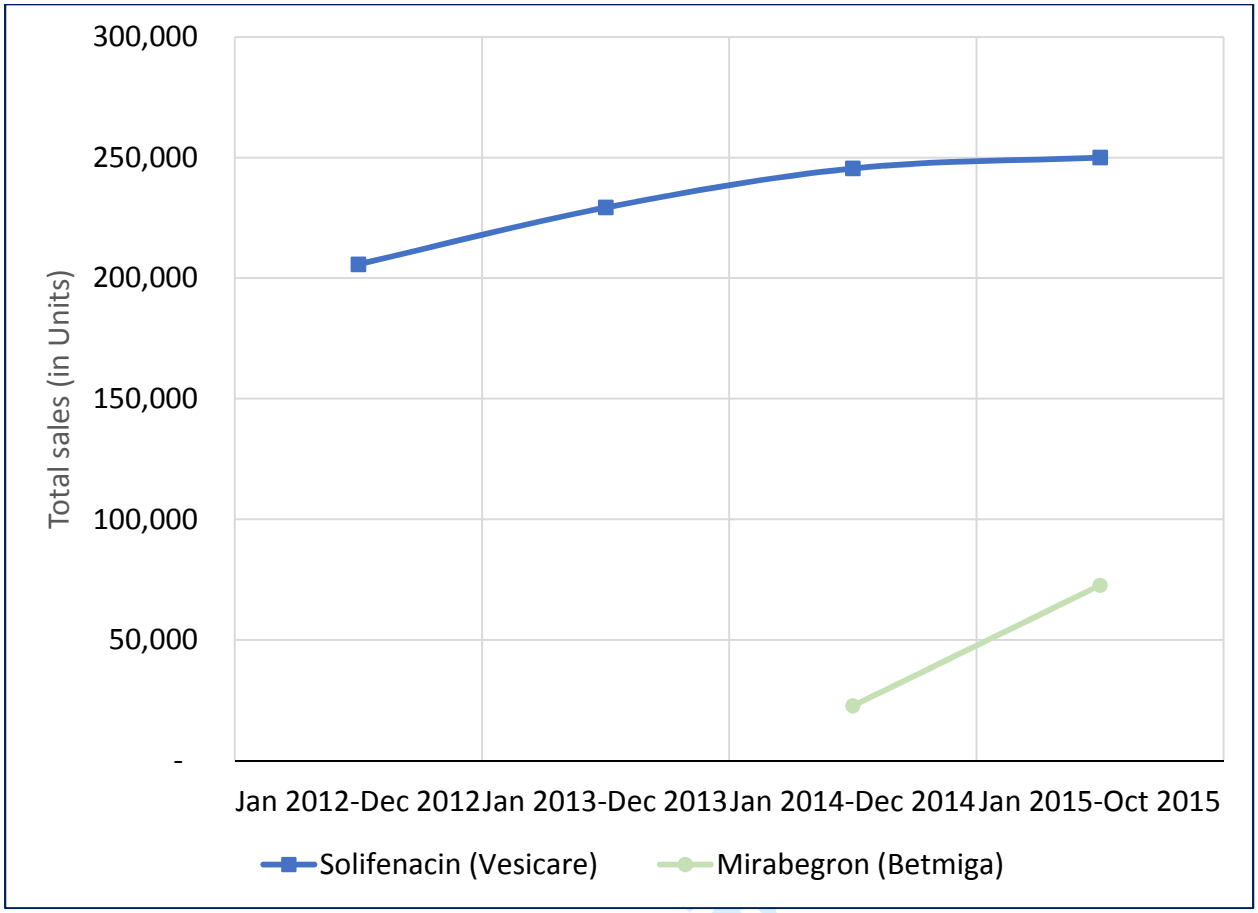
Appendix Figure 3.3: Sales of non-PBS funded overactive bladder drugs



Mirabegron: 1 unit =30 days@ 25mg/day; solifenacin: 30 days@ 5mg or 10mg/day. Source: IMS Quintiles

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 6-7; on-line appendix tables 1&2
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5-6 (drug data); On-line appendix tables 1 & 2 (event codes)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 5-6 (drug data); On-line appendix tables 1 & 2 (event codes)
Bias	9	Describe any efforts to address potential sources of bias	Page 7: coder was blinded to sponsor, attendees and event characteristics.
Study size	10	Explain how the study size was arrived at	N/A Population-based
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 5-7. Quantitative variables were based on coding above.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg	N/A

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		numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Pages 7-9 and on-line appendix
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 7-9 and on-line appendix
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Does industry-sponsored education foster overdiagnosis and overtreatment of depression, osteoporosis and overactive bladder syndrome? An Australian cohort study

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Does industry-sponsored education foster overdiagnosis and overtreatment of depression, osteoporosis and overactive bladder syndrome? An Australian cohort study

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Contributors: BM initiated the study, designed the data coding approach and plans for analysis, assisted with the development of the coding scheme, carried out analyses, and drafted and revised the paper. She is the guarantor. SS and AF contributed to the study design and coding scheme, carried out data coding and analysis, and revised the draft paper; QG, RM and LB contributed to the study design and coding scheme and revised the draft paper.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). Dr. Mintzes reports that she was an expert witness on behalf of plaintiffs in a Canadian class action suit concerning cardiovascular risks of a testosterone gel. None of the other authors report any financial relationships with organisations that might have an interest in the submitted report in the previous three years. None of the authors have received any financing from pharmaceutical manufacturers. The authors declare no other relationships or activities that could appear to have influenced the submitted work.

Transparency: As guarantor, Dr Mintzes affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Ethical approval: Not required.

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Abstract: [300 words]

Objectives: to investigate patterns of industry sponsored educational events that focus on specific health conditions for which there are concerns about overdiagnosis and overtreatment.

Design and Setting: This retrospective cohort study examines publicly reported industry-sponsored events in Australia from October 2011 to September 2015 for three conditions potentially subject to overdiagnosis and overtreatment: depression, osteoporosis, and overactive bladder. We used a database of transparency reports to identify events with a focus on depression, osteoporosis and overactive bladder and compared these with other sponsored events. We hypothesised that companies marketing treatments for each condition would sponsor related events and that target audiences would mainly work in primary care, reflecting a broad patient population.

Main outcome measures: Event and attendee characteristics, sponsoring companies, related marketed treatments, cost-effectiveness ratings and dispensing rates.

Results: Over the study period, we identified 1,567 events focusing on depression, 1,375 on osteoporosis and 190 on overactive bladder (total n= 3,132, with 96,660 attendees). These events were attended by primary care doctors more often than sponsored events without a focus on these three conditions: relative risk (RR) = 3.06 (95% CI 2.81 – 3.32) for depression, RR= 1.48 (95% CI 1.41-1.55) for osteoporosis, and RR= 2.59 (95% CI 2.09-3.21) for overactive bladder. Servier, which markets agomelatine and AstraZeneca (quetiapine) sponsored 51.2% and 23.0% of depression events respectively. Amgen and GSK, which co-market denosumab, sponsored 49.5% of osteoporosis events, and Astellas and CSL (mirabegron and solifenacin) sponsored 80.5% of overactive bladder events.

Conclusions: This 4-year overview of industry-sponsored events on three overdiagnosed and overtreated conditions found that primary care clinicians were often targeted, dinner was often provided, and that a few companies sponsored most events. In most cases, sponsors' products are not cost-effective choices for the specified condition. This pattern highlights the need for professional education to be free of commercial sponsorship.

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Strengths and limitations of this study

- Australia's transparency reports of industry funding of health professionals were unique internationally until 2015, in that the focus was on sponsored events.
- This is the first data-driven national analysis of condition-specific industry educational event sponsorship for overdiagnosed and overtreated conditions.
- Classification of events was blinded to sponsor, attendee characteristics, and event descriptions.
- For each condition, we examined trends over time in sales and dispensing of lead sponsors' relevant marketed drugs, but we could not assess causal links between increased prescribing and event attendance, as no information was publicly available on the identity of individual event participants.
- Limited detail was available on the content of sponsored events; therefore, despite a sensitive search, we may have missed some relevant events per condition

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[3414 words]

Introduction

The role of pharmaceutical industry sponsorship of health professional education has been subject to considerable controversy. There is disagreement about whether sponsored education is primarily promotional or educational. It has been described on the one hand as, "marketing masquerading as education", (1) and on the other, if accompanied by proper controls, as able to meet the goal of, "needs based, relevant, accessible education that is balanced and unbiased and improves health care outcomes." (2)

This controversy extends not only to how treatment outcomes are discussed, but also to how conditions are defined. Messages in commercially-sponsored education may exaggerate prevalence and/or attempt to medicalise aspects of ordinary life. Identified "marketing messages" in continuing medical education (CME) for low female sexual desire included statements that it is "very common and underdiagnosed", and that, "women may not be aware that they are sick or distressed." (3) Similarly, United States (U.S.) CME sponsored by a testosterone manufacturer supported a broader definition of hypogonadism than in listed indications for testosterone. (4)

A sponsored CME campaign can reach many health professionals, with potential widespread effects on practice. Purdue Pharma's launch of the opioid analgesic oxycodone in the U.S. included over 20,000 sponsored educational events, many of which targeted GPs, potentially contributing to more opioid use in primary care. (5)

These are product-specific examples of sponsored CME that received media attention and may not reflect broader trends. There has been little exploration of the link between sponsored CME and specific conditions prone to overdiagnosis. Overdiagnosis, the detection of conditions unlikely to lead to ill-health, disability or death in the absence of treatment, has been characterised as a "modern epidemic". (6, 7) It can lead to harm from adverse effects of treatments from which a person is unlikely to benefit, to psychological harm if a healthy person suffers from anxiety or stigma due to disease labelling, and to harm to society through higher healthcare costs. There is evidence of commercial influence on overdiagnosis in a range of conditions, through direct and indirect marketing aiming to establish the need for a product. (7)

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One consequence of overdiagnosis is overtreatment, as overdiagnosis expands the pool of potentially treatable patients beyond thresholds at which treatment has been shown to be beneficial. The wide ranging influence of industries that benefit from expanded markets has been highlighted as a key driver. (8)

National patterns of industry sponsorship can shed light on controversies concerning the role of sponsored CME. From 2007 to late 2015, members of Medicines Australia, the national pharmaceutical industry trade association, were required by law to report on sponsored events for health professionals. (9) These are described by Medicines Australia as "educational events" and include both accredited CME and a large range of events without accreditation. (10)

Australia was one of the first countries to require the pharmaceutical industry to publicly report financing of hospitality for health professionals. In 2007, the Australian Competition Tribunal required Medicines Australia – who at the time opposed the move – to introduce mandatory disclosure of industry-sponsored events for health professionals following recommendations by the Australian Competition and Consumer Commission (ACCC). Unlike other countries relying on industry self-regulation of drug promotion via national industry associations, Australia has a what could be described as a quasi-regulatory system, requiring approval of self-regulatory standards by a public regulatory body, the ACCC. (11)

These data provide a unique opportunity to examine the link between condition-specific sponsored events and companies marketing medicines for a condition. Over this 4-year period, 116,845 events are described, varying in scope from a half-hour journal club in a hospital meeting room to several-day conferences, sometimes held overseas. (12)

We report here on event sponsorship with a focus on three conditions highlighted in the medical literature as potentially subject to overdiagnosis and overtreatment: depression, (13) osteoporosis (14), and overactive bladder. (15) We hypothesise that companies marketing drugs for these conditions are more likely to sponsor events with a focus on that condition than other companies. We also hypothesise that these events tend to target a primary care practitioners who are likely to treat milder disease states than specialists. To test these hypotheses, we compare characteristics

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of the events focusing on these three conditions with other events sponsored by companies during the 4-year study period.

To investigate clinical implications, we examine whether sponsors' products were judged to be cost-effective and are covered under Australia's Pharmaceutical Benefits Scheme's (PBS). The PBS was introduced in 1948 to subsidise the costs of outpatient medicines for the entire Australian population. The aim is to provide affordable access to needed medicines. An expert committee, the Pharmaceutical Benefits Advisory Committee (PBAC) recommends listing of medicines based on cost-effectiveness considerations that include both therapeutic gains and price. Medicines not listed on the PBS tend to have very limited sales.

We assess sponsorship patterns per condition in terms of audience, clinical versus non-clinical setting, and provision of meals. We examined how often events included company-sponsored dinners as events with dinners provided are often held at restaurants and represent a higher-value gift. For products for which there was a shift in which company held distribution rights over the study period, we also examined timing of event sponsorship in relation to distribution rights.

Methods

Data sources

We downloaded 301 publicly available company reports covering the period October 2011 to September 2015 from the Medicines Australia website (www.medicinesaustralia.com.au), converted them from PDF into Excel files, cleaned the data and resolved discrepancies. For example, we removed text from columns that should have contained numeric values only (e.g. total cost) and, for a small minority of events, corrected totals equal to less than reported component costs.

These reports include the sponsoring company, timing, event description, venue type, number and profession of attendees, hospitality costs and total event costs. Coding methods are described in detail elsewhere. We developed a retrospective cohort of sponsored events based on timing of sponsorship per company over time. A descriptive overview of the data on sponsored events has been published, (12) and the data set used for this analysis is available at:

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http://dx.doi.org/10.4227/11/592631edbd9d5

We obtained a list of brands sold in Australia for each condition from the Australian Medicines Handbook (16) and manufacturers' websites, and annual dispensing data for publicly reimbursed drugs through Australia's Pharmaceutical Benefit Scheme (PBS) http://www.pbs.gov.au/info/browse/statistics#AS. For non PBS-subsidised drugs, sales volume data were obtained through QuintilesIMS.

We examined volume of use using annual numbers of dispensed prescriptions for PBS-subsidised drugs and numbers of units sold to retail and hospital pharmacies for non PBS-subsidised drugs.

Selection of targeted conditions

We chose depression, osteoporosis, and overactive bladder as illustrative case studies of conditions for which diagnostic thresholds and treatment have extended beyond levels at which patients are likely to benefit. We selected these conditions *a priori* before carrying out any analyses.

Depression screening leads to many false positives, (17) (18) and many patients prescribed antidepressants in primary care fail to meet diagnostic criteria for major depression, (19) a phenomenon that has been described as "medicalising sadness". (13) In 2013, Australia had one of the highest rates of antidepressant use among OECD countries. (20)

Questions have also been raised about diagnostic criteria for osteoporosis and the role of bone densitometry in greatly expanding the treatable population, primarily when used in screening of asymptomatic post-menopausal women, but also as a diagnostic tool for women with low trauma fractures. Bone density screening is poorly predictive of clinical fractures, and a focus on bone density rather than fragility fractures has led to many more diagnoses. (14) Further treatment expansion has occurred through lowered thresholds for "pre-osteoporosis" and "osteopenia", which further extend disease labelling to populations that fail to meet established criteria for a diagnosis of osteoporosis.

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An "imprecise" symptom-based definition of overactive bladder, largely linked to commercial interests, has replaced urodynamically confirmed bladder instability. (15) Tolterodine, marketed by Pharmacia, was the first drug approved for overactive bladder symptoms. In 2002, Pharmacia's Vice-President described a threefold expansion of the treatable population through a definition of overactive bladder no longer requiring urinary incontinence. (21)

Drug treatments for these three conditions have been heavily advertised to the public in the United States (US), with advertising that relies heavily on emotional appeals, targets women, and tends to blur the boundaries between normal life and medical conditions requiring treatment. (22)

Coding of Medicines Australia data on sponsored events

An initial coding scheme for industry-sponsored events included sponsoring company, location, attendee profession, clinical focus, type of hospitality (such as whether meals or travel and accommodation were provided), and a set of relevant keywords to search unstructured text. (12) We designed an additional coding scheme to identify events focusing on the three included conditions. The research team iteratively developed keywords based on disease names/symptoms and drug classes and products sold in Australia (generic and brand names) for each condition. Keywords were used to search unstructured text in the "Description of function" column of reports. All relevant keywords associated with ≥ 1 event listed in the database were retained in the final coding scheme. (On-line Appendix, Tables 1 and 2) During coding, we concealed other variables (using Excel's 'Column Hide' function) to blind the coder [SS] to sponsor, attendee characteristics, and event descriptors.

Analysis

For each included condition, we provide a detailed analysis for all companies sponsoring at least 5% of events. We examined whether these companies market drugs to treat the condition, and PBS reimbursement status for these drugs. We present frequency tables for event and attendee characteristics. Costs are reported in AUD$. We performed chi square analyses to compare events per condition with other sponsored events using SPSS-Version 22.

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Results

Over the 4-year study period, we identified 3,132 events focusing on the three conditions, with 96,620 attendees. This included 1,567 events with a focus on depression, with 41,474 attendees; 1,375 on osteoporosis with 33,916 attendees; and 190 on overactive bladder with 21,270 attendees. As no individuals are named, we could not ascertain numbers of repeat attendees. Table 1 summarises event characteristics. Events focusing on these conditions represent 2.7% of sponsored events (n=116,845) over the 4-year period, and 2.8% of attendees (n=3,481,750). (12)

For all three conditions, the median number of event attendees (19-20) was similar to sponsored events in general. (12) For all three conditions, events were held less often in a clinical setting (hospital or clinic) than other sponsored events: RR = 0.51 (95% CI 0.50-0.53) for depression; RR = 0.72 (95% CI 0.68-0.76) for osteoporosis; RR= 0.47 (95% CI 0.43-0.50) for overactive bladder. Nurses were only at 24.4% of condition-focused events compared with 39.6% of total events, (12) likely reflecting the less frequent hospital setting. However, attendees were more likely to be primary care physicians (GPs or family medicine) than at other events: relative risk (RR) = 3.06 (95% CI 2.81 – 3.32) for depression, RR= 1.48 (95% CI 1.41-1.55) for osteoporosis, and RR= 2.59 (95% CI 2.09-3.21) for overactive bladder. Depression and osteoporosis events were also more likely to feature a dinner than other events: RR= 1.73 (95% CI 1.64-1.82) for depression and RR = 1.33 (95% CI 1.27-1.38) for osteoporosis. This trend was not seen for overactive bladder.

The median cost per attendee was higher than for events in general (AUD$14): AUD$104 for depression, AUD$52 for osteoporosis, and AUD$85 for overactive bladder. (Table 1)

A few companies sponsored most of these condition-focused events. Figure 1 provides an overview of companies sponsoring ≥ 5% of events. All sell at least one drug for the relevant indication. Table 2 provides an overview of these drugs' PBS funding status. We present illustrative event descriptions featuring brand names in Table 3, with added details on sponsored events per company in on-line appendix Table 3.

Depression-related events

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Two companies sponsored > 80% of depression-related events: Servier (51.2% of events), which markets the antidepressant agomelatine and AstraZeneca (23.0% of events), which markets the antipsychotic quetiapine. The extended-release formulation of quetiapine (brand name Seroquel XR) is approved for depression treatment in patients intolerant to other therapies or with inadequate response. Neither agomelatine nor the depression indication for quetiapine are PBS-subsidised. Pfizer, which markets five PBS-subsidised antidepressants (desvenlafaxine, venlafaxine, sertraline, reboxetine, doxepin), was the next most frequent sponsor (16.0% of events).

We examined agomelatine and quetiapine sales volumes over the study period. Agomelatine sales tripled, from 99,625 units in 2012 to 300,103 units in 2015 (28 days treatment/unit). Sales of the extended-release formulation of quetiapine increased from 247,374 units in 2012 to 374,917 in 2015 (60 days treatment/unit). Sales of other AstraZeneca quetiapine formulations decreased over the same period, from 499,445 units sold in 2012 to 202,783 in 2015. (23) (on-line Appendix, Figure 3.1)

Seventy-nine AstraZeneca events focused on 'the anxious depressed patient'. Figure 2 is an invitation for one of these events, featuring the same image that was used in an advertisement for extended-release quetiapine that appeared in the *Medical Journal of Australia*. This formulation of quetiapine is also indicated for generalised anxiety disorder.

Osteoporosis-related events

Osteoporosis event sponsorship, similarly, was highly concentrated: Amgen and GSK, which co-market denosumab sponsored 31.3% and 18.1% of events respectively (in total, 49.4%). Novartis, which markets zoledronic acid, and oestradiol/norethisterone, a hormone therapy approved for osteoporosis prevention in high-risk women intolerant of other products, sponsored 19.9% of events; Servier, which markets strontium sponsored 15.0%; and Sanofi, which marketed risedronic acid until December 2014, sponsored 8.7%. Denosumab, zoledronic acid, oestradiol/norethisterone, and risedronic acid are PBS-subsidised; strontium was delisted in August 2016 due to cardiac risks.

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Sanofi transferred its marketing rights for risedronate to Actavis in December 2014. (24) Sanofi sponsored no osteoporosis events from October 2014 onwards. (on-line appendix Figure 3.2)

Denosumab dispensations increased nearly 7-fold over the study period, from 45,220 in 2012 to 309,350 in 2015. (25) Risedronate, zoledronic acid and strontium dispensations all decreased (on-line appendix, Figure 3.3) Of 193 events mentioning denosumab's brand name, Prolia, 104 were sponsored by Amgen and 88 by GSK.

Overactive bladder-related events

Two companies dominated sponsorship of overactive bladder events: Astellas (40.5% of events), which markets mirabegron and solifenacin, the latter after October 2014, and CSL (40.0% of events), which marketed solifenacin from February 2011 to October 2014. Neither drug is PBS-subsidised. Astellas did not request PBS reimbursement for mirabegron. PBAC rejected solifenacin in 2007, judging benefits and cost-effectiveness to be uncertain.

All CSL-sponsored overactive bladder events occurred while the company held distribution rights for solifenacin, e.g. to October 2014; most Astellas-sponsored events were held from 2014 onwards, when it obtained marketing rights. (on-line appendix Figure 3.4) Both solifenacin and mirabegron sales increased over the study period. (on-line appendix, Figure 3.5)

Discussion

In this analysis of 3,132 Australian pharmaceutical industry-sponsored events with 96,660 attendances, focusing on three clinical conditions prone to overdiagnosis, we found a strong concentration of sponsorship among few companies. Two companies sponsored over 70% of depression events; another two companies over 80% of overactive bladder events. In osteoporosis, the two companies that co-market denosumab sponsored nearly 50% of events.

Several products marketed by key event sponsors were considered unacceptable for PBS reimbursement, and are associated with cost, efficacy and safety concerns that have been flagged internationally. Servier, which sponsored over half of depression-related events, sells agomelatine, which is not PBS-subsidised. Agomelatine is not approved in the U.S. or Canada. A

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French independent drug bulletin, *Prescrire*, characterized the drug as "more dangerous than useful" and called for its withdrawal in 2015. (26) A Spanish bulletin, similarly, considered it, "worse than first-line antidepressants, up to 15-fold more expensive, and a worrying hepatic safety profile."(27)

A 2012 Cochrane systematic review found that AstraZeneca's atypical antipsychotic quetiapine had limited efficacy evidence for depression. (28) An updated systematic review, published in 2015, concluded that quetiapine had not been shown to improve function and that methodological biases had exaggerated benefits and minimised harm. (29)

Like agomelatine, denosumab is on the French bulletin *Prescrire*'s list of 71 drugs to avoid in 2016 because of "a disproportionate risk of adverse events" including serious infections due to immunosuppression, with only modest efficacy. (30) In 2015, half of all new Australian osteoporosis prescriptions were for denosumab. (31)

All anticholinergic overactive bladder drugs, including solifenacin, have modest benefits, preventing one incontinence episode on average every two days, with frequent dry mouth and constipation, and there is observational evidence of dementia risk with longer-term use. (32) Mirabegron has similar efficacy to anticholinergics (32) and can lead to severe hypertension. (33)

This analysis is limited by the data available. Our analysis only includes 2.7% of events, a likely underestimate as not all event descriptions mention a condition. These three conditions are illustrative case studies and cannot be assumed to represent all condition-related sponsored events. A variety of influences are expected to affect sales trends, including a large range of promotional activities. Sponsored events represent only one aspect of broader promotional campaigns to promote sales. (34) However, a strength of this analysis is that it covers all sponsored events in Australia over four years, and coding was blinded to sponsor identity, types of attendees, gifts and costs. Due to the unique Australian dataset, this is the first such data-driven national analysis to examine condition-specific event sponsorship.

Company reports on financing of sponsored events provided limited information on content, leaving many questions unanswered. More research is needed on the messages in sponsored

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education, including on thresholds for disease diagnosis and treatment. Additionally, as individuals were not named, we could not directly evaluate the link between event attendance and individual prescribing patterns.

We could only examine potential contributions to overdiagnosis and overtreatment indirectly. We had hypothesized that events would focus on primary care, reflecting milder disease states. This is a hypothesized association only; we could not directly assess whether the messages in these events promote overdiagnosis or overtreatment. However, nearly two-thirds of events, 62%, for the three conditions were attended by primary care doctors, versus 21% of other events. The focus on primary care was most pronounced for depression events: 74%.

The concentration of sponsorship by companies marketing products subject to safety, cost and efficacy concerns raises questions about influences on prescribing choice. This pattern is consistent with Brody and Light's hypothesis of an "inverse benefit law", in which intense marketing of drugs that may benefit a small proportion of patients is harmful to public health because a broader patient population is targeted than is likely to benefit. (35)

Many of these condition-focused events included dinner and were held in non-clinical settings such as restaurants. Costs per person were higher than for events in general. Even small gifts, such as food and drink, can affect behaviour. (36) An analysis of U.S. transparency reports found that physicians who receive ≥ 1 sponsored meal with a mean value of < US $20 were more likely to prescribe the promoted product, with larger effects observed the more meals received. (37) We examined whether overseas travel may have been responsible for higher median costs. In total (n=117,845), 1.9% of events were held overseas, and as expected, these events had the highest per person costs. However, only 0.1% of depression-related events, 0.4% of osteoporosis-related events and no overactive bladder events were held overseas. Therefore, this is an unlikely explanation. Travel costs within Australia are not reported separately from other hospitality costs, so we could not examine their contribution to overall costs.

Timing of sponsorship was linked to when a company sold a drug to treat the included condition, consistent with a sales orientation. Companies discontinued event sponsorship of overactive bladder and osteoporosis events when they no longer had marketing rights for a product for these

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conditions. This promotional orientation is consistent with internal documents released during the U.S. legal case on gabapentin, which described the use of CME to market off-label use. (38)

In this 4-year overview of industry-sponsored events focusing on depression, osteoporosis and overactive bladder, we found concentrated sponsorship among few companies per condition. These companies mainly market products that are not considered cost-effective choices for the specified conditions. This raises concerns about impacts on prescribing quality and on national prescribing trends. There was a strong focus on primary care physicians, frequent provision of dinner, and non-clinical setting. Although a focus on primary care does not necessarily imply promotion of overdiagnosis, promotion in primary care is consistent with a focus on a broader rather than narrower patient population. This observed pattern of event sponsorship raises concerns about the role of industry-sponsored education in conditions identified as prone to overdiagnosis, and highlights the need for ensure that professionals have ready access to continuing professional education that is free of commercial sponsorship.

Figure legends:

Figure 1:Percent of events sponsored by each company, in total and per condition*

Figure 2: Invitation for an AstraZeneca sponsored event

Acknowledgements: The authors would like to thank QuintilesIMS for their assistance in providing data on pharmaceutical sales volumes in Australia.

Access to the data: All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Previous presentations: Preliminary study results were presented at the *Preventing Overdiagnosis* conference in Barcelona, Spain, September 2016.

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References

1. Moynihan R. Doctors' education: the invisible influence of drug company sponsorship. BMJ. 2008;336(7641):416-7.

2. Marlow B. Is continuing medical education a drug-promotion tool?: NO. Canadian Family Physician. 2007;53(10):1650-2, 4-6.

3. Meixel A, Yanchar E, Fugh-Berman A. Hypoactive sexual desire disorder: inventing a disease to sell low libido. J Med Ethics. 2015;41(10):859-62.

4. Fauber J, Jones C, Fiore K. Slippery Slope: Testosterone Muscles Its Way to Profits. Medpage Today. October 18, 2015. Available at: http://www.medpagetoday.com/special-reports/slipperyslope/54156 Accessed January 17, 2017.

5. Spithoff S. Industry involvement in continuing medical education: time to say no. Canadian Family Physician. 2014;60(8):694-6, 700-3.

6. Hoffman JR, Cooper, R.J. Overdiagnosis of disease: a modern epidemic. Arch Intern Med. 2012;172(15):1123-4.

7. Moynihan R, Heath I, Henry D. Selling sickness: the pharmaceutical industry and disease mongering. BMJ.2002;324(7342):886-91.

8. Moynihan R, Doust J, Henry D. Preventing overdiagnosis: how to stop harming the healthy. BMJ 2012; 344:e3502 doi: 10.1136/bmj.e3502

9. Monk D. Improving transparency in the pharmaceutical industry. Australian Prescriber. 2016;39(4):110-111.

10. Robertson J, Moynihan R, Walkom E, Bero L, Henry D (2009) Mandatory Disclosure of Pharmaceutical Industry-Funded Events for Health Professionals. PLoS Med 6(11): e1000128. doi:10.1371/journal.pmed.1000128

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

11. Medicines Australia, Code of Conduct Edition 18, 2015. https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/01/20150617-PUB-Code-Edition-18-FINAL.pdf

12. Fabbri A, Grundy, Q, Mintzes B, et al. Pharmaceutical industry-funded events for health professionals: An analysis of data released under Australian transparency rules. BMJ Open 2017;7:e016701. doi:10.1136/ bmjopen-2017-016701

13. Dowrick C, Frances A. Medicalising unhappiness: new classification of depression risks more patients being put on drug treatment from which they will not benefit. BMJ. 2013;347.

14. Jarvinen TL, Michaelsson K, Jokihaara J, et al. Overdiagnosis of bone fragility in the quest to prevent hip fracture. BMJ. 2015;350:h2088.

15. Tikkinen KA, Auvinen A. Does the imprecise definition of overactive bladder serve commercial rather than patient interests? Eur Urol. 2012;61(4):746-8.

16. Australian Medicines Handbook. Adelaide, Australia: AMH; 2016.

17. Jerant A, Kravitz RL, Fernandez YGE, et al. Potential antidepressant overtreatment associated with office use of brief depression symptom measures. J Am Board Fam Med. 2014;27(5):611-20.

18. Mitchell AJ VA, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. Lancet. 2009;374:609–19.

19. Wong J MA, Eguale T, Buckeridge DL, Abrahamowicz M, Tamblyn R. Treatment Indications for Antidepressants Prescribed in Primary Care in Quebec, Canada, 2006-2015. JAMA 2016; 315(20):2230-1.

20. Organisation for Economic Cooperation and Development (OECD). Health at a Glance 2015: How does Australia compare? Available at: https://www.oecd.org/australia/Health-at-a-Glance-2015-Key-Findings-AUSTRALIA.pdf Accessed January 16, 2017.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

21. Elliott C. White Coat, Black Hat. Adventures on the Dark Side of Medicine. Boston, MA, USA: Beacon Press; 2010.

22. Mintzes B. 'Ask your doctor'. Women and direct to consumer advertising. Chapter 2: 15-46. In: Ford AR and Sabil D (eds). The Push to Prescribe. Women & Canadian Drug Policy. Toronto: Women's Press. 2010.

23. QuintilesIMS. Quetiapine Fumarate unit sales in Australia, 2012 to 2015. *Data provided to authors on request by QuintilesIMS, November 2016.*

24. Actavis takes back Actonel December 12, 2014. Available at: https://pharmadispatch.com/news/actavis-takes-back-actonel Accessed January 9, 2017.

25. Pharmaceutical Benefits Scheme. Australian Department of Health. ASM_Table_1. Australian Statistics on Medicine. 2012 to 2015. Available at: https://www.pbs.gov.au/info/browse/statistics - Expenditure2016 Accessed January 25, 2017.

26. Prescrire Editorial Staff. Pour mieux soigner, des médicaments à écarter : bilan 2015. La Revue Prescrire. 2015;35(376):144-51.

27. Anonymous. Agomelatine (Valdoxan). Worse than first-line antidepressants, up to 15-fold more expensive, and a worrying hepatic safety profile. Drug Assessment Report Drug and Therapeutics Bulletin of Navarre. DAR no. 3. 2010. Available at: http://www.navarra.es/home_en/Temas/Portal+de+la+Salud/Profesionales/Documentacion+y+publicaciones/Publicaciones+tematicas/Medicamento/FET/2010/DAR+No+3+Agomelatine.htm Accessed January 25, 2017.

28. Komossa K, Depping, AM, Gaudchau A et al. Second-generation antipsychotics for major depressive disorder and dysthymia. . Cochrane Database of Systematic Reviews. 2010;12.

29. Therapeutics Initiative. Antipsychotics should not be used for non-psychotic depression. Therapeutics Letter 95. September 30, 2015. Available at: http://www.ti.ubc.ca/2015/09/30/antipsychotics-should-not-be-used-for-non-psychotic-depression/ Accessed January 16, 2017.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

30. Prescrire Editorial Staff. Towards better patient care: drugs to avoid in 2016. Prescrire International. 2016;25(170):105-11.

31. McColl G. Chair, Drug Utilisation Sub Committee. Drug Utilisation Committee Outcome Statement 29-30 September 2016. Canberra, Australia. Pharmaceutical Benefits Advisory Committee, Pharmaceutical Benefits Service. 2016. Available at: http://www.pbs.gov.au/industry/listing/elements/dusc-meetings/dos/dusc-dos-sep-2016.pdf Accessed January 16, 2017.

32. Therapeutics Initiative. Are claims for newer overactive bladder drugs warranted? Therapeutics Letter 93, April 22, 2015. Available at: http://www.ti.ubc.ca/2015/04/22/are-claims-for-newer-drugs-for-overactive-bladder-warranted/ Accessed January 26, 2017.

33. Medicines and Health Products Regulatory Agency, UK. Mirabegron (Betmiga▼): risk of severe hypertension and associated cerebrovascular and cardiac events. Drug Safety Update. 14 October, 2015. Available at: https://www.gov.uk/drug-safety-update/mirabegron-betmiga-risk-of-severe-hypertension-and-associated-cerebrovascular-and-cardiac-events Accessed January 20, 2017.

34. Gagnon MA, Lexchin J (2008) The cost of pushing pills: A new estimate of pharmaceutical promotion expenditures in the united states. PLoS Med 5(1): e1. doi:10.1371/journal.pmed.0050001

35. Brody H, Light DW. The Inverse Benefit Law: How Drug Marketing Undermines Patient Safety and Public Health. American Journal of Public Health. 2011;101(3):399-404.

36. Dana J, Loewenstein G. A Social Science Perspective on Gifts to Physicians From Industry. JAMA. 2003;290(2):252-5.

37. DeJong C, Aguilar T, Tseng C, Lin GA, Boscardin W, Dudley R. Pharmaceutical industry–sponsored meals and physician prescribing patterns for medicare beneficiaries. JAMA Internal Medicine. 2016;176(8):1114-10.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

38. Steinman MA, Bero LA, Chren M, Landefeld C. Narrative review: The promotion of gabapentin: an analysis of internal industry documents. Ann Intern Med. 2006;145(4):284-93.

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Table 1: Characteristics of sponsored events for the three conditions

	Total events n=116,845	Depression n=1,567	Osteoporosis n=1,375	Overactive bladder n=190
Attendees				
Total number of attendees (% of total)	3,481,750	41,472 (1.2%)	33,916 (1.0%)	21,270 (0.6%)
Median/ event (IQR)	18 (12-25)	19 (12-28)	19 (12-27)	20 (13-34)
Clinicians present (% of events)				
Medical specialists	80,060 (68.5%)	839 (53.5%)	921 (67.0%)	50 (26.3%)
Primary care doctors	24,662 (21.1%)	1,159 (74.0%)	638 (46.4%)	132 (69.5%)
Trainees	44,774 (38.3%)	222 (14.2%)	531 (38.6%)	18 (9.5%)
Nurses	46,214 (39.6%)	357 (22.8%)	359 (26.1%)	46 (24.2%)
Types of medical specialists present (% of events)				
Most frequent	Oncology 19,723 (16.9%)	Psychiatry 804 (51.3%)	Endocrinology 516 (37.5%)	Urology 30 (15.9%)
Second	Surgery 10,670 (9.1%)	Geriatrics 55 (3.5%)	Rheumatology 190 (13.8%)	Ob/Gyn 13 (6.8%)
Expenses (AUD$)				
Total cost of events	$286,117,928	$6,259,581(2.2%)	$6,073,333(2.1%)	$568,332 (0.2%)
Median cost per event (IQR)	$263 ($153-1,195)	$1,941 ($659–3,264)	$686 ($217-2,500)	$2,012 ($765-3,370)
Median cost per head (IQR)	$14 ($10-68)	$104 ($48-141)	$52 ($13-119)	$85 ($31-90)
Food & drink cost (% of total cost)	$84,862,791 (30%)	$2,441,950 (39%)	$2,314,319 (38%)	$233,548 (41%)
Median per event food & drug cost (IQR)	$197 ($107-405)	$911 ($135– 1,712)	$337 ($150 - 1,478)	$1,115 ($91-1868)
Median per head food & drink cost (IQR)	$12 ($8-20)	$57 ($11-77)	$17 ($11-75)	$55 ($11-80)
Event characteristics				
Clinical setting	74,998 (64.2%)	487 (31.1%)	692 (50.3%)	44 (23.2%)
Any food provided	105,667(90.4%)	1441 (92.0%)	1298 (94.4%)	158 (83.2%)
Dinner	19,873 (17.0%)	811 (51.7%)	512 (37.2%)	41 (21.6%)
Lunch	25,935 (22.2%)	241 (15.4%)	485 (35.3%)	28 (14.7%)
Tea	14,067 (12.0%)	15 (1.0%)	69 (5.0%)	2 (1.1%)
Breakfast	12,806 (11.0%)	24 (1.5%)	77 (5.6%)	7 (3.7%)
All-day event meals	3,113 (2.7%)	62 (4.0%)	58 (4.2%)	1 (0.5%)
Unspecified	29,873 (25.6%)	288 (18.4%)	97 (7.1%)	79 (41.6%)

Abbreviations: IQR = interquartile range

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Table 2: Pharmaceutical Benefits Scheme (PBS) subsidy of drugs marketed for depression, osteoporosis, and overactive bladder marketed by sponsoring companies

Company	Drug for condition (brand)	PBS subsidy?(Y/N)	PBAC decisions and rationale for restrictions	Notes
Depression				
Servier	Agomelatine (Valdoxan)	No	Nov 2010: uncertainty; inappropriate comparator July 2011, March 2012: superior clinical effectiveness and safety over SSRIs not demonstrated	
AstraZeneca	Quetiapine (Seroquel XR)[a]	No for MDD, treatment-resistant depression or anxiety disorders.	Nov 2011: inadequate clinical evidence to support superiority. July 2013: non-inferior comparative safety and effectiveness not established	Quetiapine is PBS-funded for schizophrenia; acute mania & bipolar disorder
Pfizer	Desvenlafaxine (Pristiq)	Yes	Nov 2008: *cost minimisation*[b] vs. venlafaxine; no evidence of therapeutic advantage.	
	Venlafaxine (Efexor-XR, Altven),Sertraline (Zoloft),Reboxetine (Edronax),Doxepin (Sinequan)	Yes	*General schedule*[c] listings, major depressive disorder.	
Osteoporosis				
Amgen and GSK	Denosumab (Prolia)	Yes	July 2010: *cost-minimisation*[b] vs. zoledronic acid Nov 2011: *Streamlined Authority*[d] , post-menopausal osteoporosis, age 70+, BMD T-score ≤ -2.5; cost-minimisation vs. alendronate July 2013: superiority vs. zoledronic acid rejected; non-inferiority accepted	2009: co-commercialised by Amgen and GSK; Dec 2015: Amgen reacquires all marketing rights in Australia.
Novartis	Zoledronic acid (Aclasta)	Yes	July 2008: *Authority Required* [e] cost-minimisation vs. alendronate; Nov 2008: listing extended: women aged 70+; BMD T-score ≤-3.0 Nov 2009: extended to men July 2011: 3-year limit removed; listing changed to *Streamlined Authority*	
	Oestradiol/ norethisterone (Estalis continuous)	Yes	*General Schedule*[c]	
Servier	Strontium (Protos)	No (previously subsidised)	July 2015: restricted to severe established osteoporosis,	

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Company	Drug for condition (brand)	PBS subsidy?(Y/N)	PBAC decisions and rationale for restrictions	Notes
			patients unable to use other drugs, without cardiovascular contraindications Aug 2016: delisted due to cardiac risks	
Sanofi	Risedronic acid (Actonel, Actonel Ec, Actonel Ec Combi, Actonel Ec Combi D)	Yes	Feb 2001: postmenopausal osteoporosis; minimal fracture trauma; *cost-minimisation* vs. alendronate Dec 2001 - extended to corticosteroid-induced osteoporosis March 2013: extended to patients aged 70 + BMD T-score ≤ -2.5	Dec 2014: Sanofi transfers marketing rights to Actavis
Overactive bladder				
Astellas	Mirabegron (Betmiga)	No	N/A. No request made for PBS listing	
CSL and Astellas	Solifenacin (Vesicare)	No	July 2007: uncertain clinical benefit and cost-effectiveness	Feb 2011 – Oct 2014: marketed by CSL Oct 2014: Astellas regains marketing rights

a. Immediate release quetiapine products are not indicated for major depressive disorder (MDD) or general anxiety disorder, only Seroquel XR.
b. *Cost-minimisation*: product is considered non-inferior in safety and efficacy to listed comparator; no higher pricing allowed.
c. *General Schedule:* no prior authority required.
d. *Streamlined Authority*: no prior approval required, but a streamlined authority code is required on the prescription; if quantities and/or repeats exceed specified levels, treated as *Authority Required*.
e. *Authority Required*: telephone or written approval required from Department of Health prior to prescribing.

Abbreviations: BMD = bone mineral density; GSK= GlaxoSmithKline; MDD = major depressive disorder; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme

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Table 3: Illustrative examples of verbatim descriptions of sponsored events

Sponsor	Date	Event content	Venue	Professionals Present	Hospitality	Total Cost
Servier	05/12	120 minute presentation including a discussion on Valdoxan specific patient cases	The Sebel Resort, Windsor, NSW	26 Advanced Trainees, Hospital Pharmacists, Psychiatrists	Dinner, including alcoholic and non-alcoholic beverages	$4138.84
Astrazeneca	08/14	Educational dinner meeting for General Practitioners with a specialist presentation on The Anxious Depressed Patient. 1 hour educational content	Kimberly Gardens St Kilda East VIC	35 GPs, Psychiatrists	Dinner with alcoholic and non alcoholic beverages	$3,750.00
GSK	06/15	HCP Osteoporosis presentation. Providing HCPs with the confidence to switch appropriate patients from bis-phosphonates to Prolia. GSK was not responsible for organising the educational content. Duration of Educational Content: 2 hour	GG Restaurant, 105 Yarra St, Geelong VIC 3220	38 GPs, Endocrinologists	Three Course Dinner, Juice / Water, Non Alcoholic Beverage, Alcoholic Beverage	$4,136.5
Astellas	04/14	Educational Dinner Meeting. Prof Philip Van Kerrebroeck giving educational launch presentation on BETMIGA, the new oral treatment in the management of Over Active Bladder. One hour educational content.	The Terrace Room (Private Dining), L'Aqua, Sydney, NSW	10 leading specialists with an interest in OAB - especially Urologists	Food & Beverages	$11,742.95

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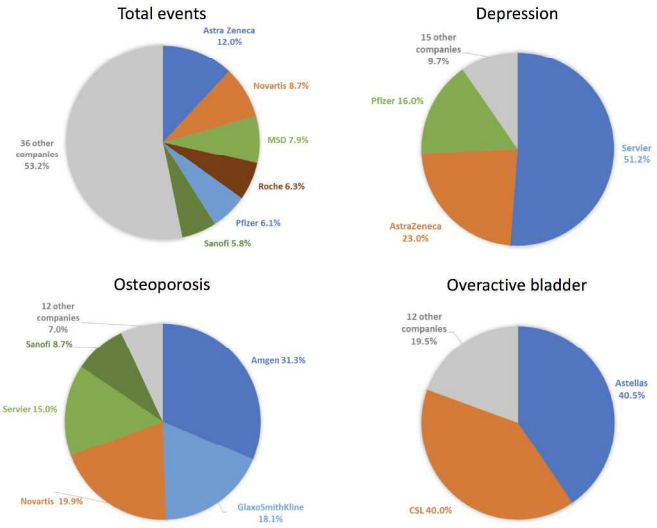

Figure 1: Percent of events sponsored by each company, in total and per condition (companies sponsoring ≧5% of events listed individually)

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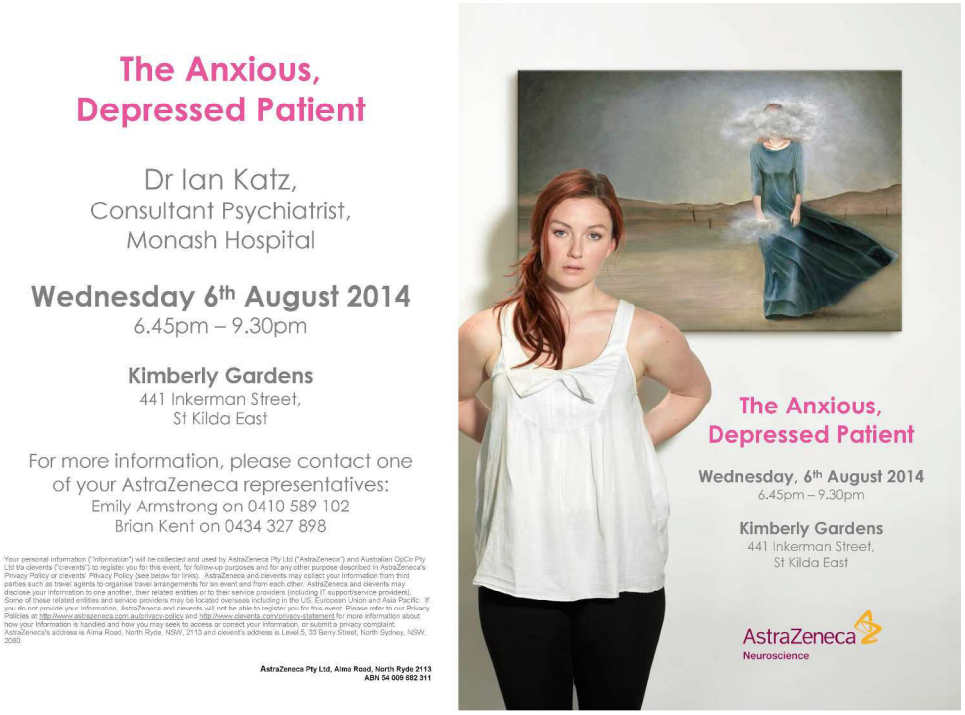

Figure 2: Invitation for an AstraZeneca sponsored event

Available at : http://ajmf.org.au/wp-content/uploads/2014/07/AJMF-VIC-Aug-2014-meeting-Kimberly-Gardens2.pdf. Accessed October 25, 2017. An advertisement with the same image ran in the May 20, 2013 issue of the Medical Journal of Australia.

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On-line Appendix:

Mintzes et al. Does industry-sponsored education foster overdiagnosis and overtreatment of depression, osteoporosis and overactive bladder syndrome? An Australian cohort study

Appendix Table 1:
Coding of event characteristic and audience variables

Variable name	Keyword search
COMPANY	A. Menarini Australia Pty Ltd; Abbott Australasia Pty Ltd OR AbbVie Pty Ltd; Actelion Pharmaceuticals Australia Pty Ltd; Alexion Pharmaceuticals Australasia PTY LTD; Allergan Australia Pty Ltd; Amgen Australia; Astellas Pharma Australia Pty Ltd; Astrazeneca Pty Ltd; Baxter Healthcare Pty Ltd; Bayer Australia Ltd; Besins Healthcare Australia; BioCeuticals; Biogen Idec Australia Pty Limited; Boehringer Ingelheim Pty Limited; Bristol-Myers Squibb Australia Pty Limited; Celgene Pty Ltd; CSL (includes also bioCSL Australia Pty Ltd and CSL Behring); Eisai Australia Pty Ltd; Eli Lilly Australia Pty Ltd; Fresenius Kabi Australia; Gilead Sciences Pty.; GlaxoSmithKline Australia Pty Ltd *+ (GSK); iNova Pharmaceuticals (Aus) Pty Ltd; IPSEN Pty Ltd; Janssen; LEO Pharma Pty Ltd; Lundbeck Australia; Merck Serono Australia Pty Ltd; MSD Australia Pty Ltd; Mundipharma Pty Ltd; Mylan EPD; Norgine Pty Limited; Novartis Pharmaceuticals Australia Pty Limited (includes also Alcon Laboratories); Novo Nordisk Pharmaceuticals; Pfizer Australia; Roche Products Pty Limited; Sanofi/Sanofi Aventis Australia Pty Ltd; Servier Laboratories (Australia) Pty Ltd; Shire Australia; Takeda Pharmaceuticals Australia Pty Ltd (includes also Nycomed Pty Ltd Report); UCB Pharma; Vifor Pharma Pty Ltd
LOCATION	
New South Wales	NSW, New South Wales, Sydney, other cities or suburbs, and postal codes of NSW*
Victoria	VIC, Victoria, Melbourne, other cities or suburbs and postal codes of VIC*
Australian Capital Territory	ACT, Australian Capital Territory, Canberra, other cities or suburbs, and postal codes of ACT*
Western Australia	WA, Western Australia, Perth, other cities or suburbs, and postal codes of WA*

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Variable name	Keyword search
South Australia	SA, South Australia, Adelaide, other cities or suburbs, and postal codes of SA*
Northern Territory	NT, North Territory, other cities or suburbs, and postal codes of NT*
Tasmania	TAS, Tasmania, Hobart, other cities or suburbs, and postal codes of Tasmania*
Overseas	Overseas: outside of Australia**
*Where the state or capital was not listed, events were hand coded based on postal codes, cities or suburbs **Events not taking place in an Australian state were hand-coded	
MEALS	
• Lunch	Lunch
• Dinner	Dinner
• Breakfast	Breakfast
• Tea	Afternoon tea, morning tea, light refreshments, light meals, sandwiches & drinks, coffee cart, snack and beverage, sushi
• All day events w/ meals	Day delegate package*; conference package**
• Food unspecified	food & beverages, meals, drinks, in hospital catering, beverages, wine
• No meals provided	Sponsorship/accommodation only, no hospitality provided, travel/accommodation only (domestic events)
*Note: “day delegate package” consisted of entries where multiple meals were listed ((Lunch, tea), (Breakfast, tea), (Dinner, tea), (Breakfast, lunch, tea)) **Note: “conference package” consisted of events lasting multiple days and typically included a day delegate package, often accommodation (food and beverage not reported separately), registration (food and beverage not reported separately), or travel (including flights, registration, airfares, accommodation and food and beverages not reported separately)	
EVENTS HELD IN CLINICAL SETTING	Hospital; clinic; practice; medicare local; health centre; surgery; medical centre; medical; health care centre; specialist centre; cancer centre; cancer care centre; heart centre; medical and dental centre; endocrine centre; radiotherapy centre; radiation centre; optical centre; eye centre; renal unit; ward; department; dept; community health; family planning; education centre.
PROFESSIONAL STATUS	
• Primary care doctors	GP; general practitioner; family medicine.

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Variable name	Keyword search
• Nurses	Nurse
• Pharmacists	Pharmacist
• Trainees	Registrar; resident; intern; student; advanced trainee; RMO; resident medical officer; JHO; SHO; senior house officer; PHO; principal house officer; fellow
• Specialty care	Specialist; consultant; senior medical officer; SMO; visiting medical officer; VMO; general medicine; general physician; *ology physician; *ology doctor; allergist; allergy physician; anesthesiologist; anesthetist; anaesthesiologist; anaesthetist; andrologist; cardiologist; dermatologist, diabetologist; emergency physician; emergency medicine physician; endocrinologist; epileptologist; gastroenterologist; geriatrician; getriatric physician; gynaecologist; obstetrician; OB/GYN; haematologist; hematologist; hepatologist; immunologist; infectious disease physician; infectious disease doctor; internal medicine physician; microbiologist; neonatologist; neurologist; nuclear medicine physician; nephrologist; renal physician; renal doctor; urologist; oncologist; pharmacologist; pulmonologist; psychogeriatrician; ophthalmologist; rheumatologist; radiologist; respiratory physician; respiratory medicine physician; respiratory medicine doctor; palliative care physician; pathologist; sexual health physician; sexual health doctor; psychiatrist; psychiatry doctor; paediatrician; surgeon; surgery doctor; intensive care doctor; intensivist; intensive care physician; cardiothoracic
CLINICAL FOCUS	
• Allergy/Immunology	Allergist; allergy; immunologist; immunology
• Anaesthesiology	Anesthesiologist; anesthetist; anaesthesiologist; anaesthetist; anaesthesiology
• Andrology	Andrologist
• Cardiology	Cardiologist; cardiology
• Dermatology	Dermatologist; dermatology
• Emergency	Emergency
• Endocrinology	endocrinologist; endocrinology; diabetologist; diabetology; diabetes
• Gastroenterology	Gastroenterologist; gastroenterology; Hepatologist; hepatology
• Geriatrics	Geriatrician; geriatric; psychogeriatrician; elderly
• Haematology	Haematologist; haematology; hematology; hematologist

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Variable name	Keyword search
• Infectious Diseases	Infectious disease; microbiologist; microbiology
• Internal Medicine	Internal medicine
• Intensive care	Intensive care; intensivist; critical care
• Neonatology	Neonatologist; neonatology; NICU; neonatal
• Nuclear medicine	Nuclear medicine
• Nephrology	Nephrologist, nephrology; renal; kidney
• Neurology	Neurologist; neurology; epileptologist
• Obstetrics/Gynaecology	Gynaecologist; gynaecology; obstetrician; OB/GYN; obstetrics
• Oncology	Oncologist; oncology; cancer
• Ophthalmology	Ophthalmologist; ophthalmology
• Otolaryngology	Otolaryngology
• Palliative care	Palliative care
• Pathology	Pathologist; pathology
• Pharmacology	Pharmacologist; pharmacology
• Paediatrics	Paediatrician; paediatric*; pediatric*
• Psychiatry	Psychiatrist; psychiatry; mental health
• Radiology	Radiologist; radiology
• Rheumatology	Rheumatologist; rheumatology
• Respiratory medicine	Lung specialist; respiratory; pulmonologist
• Sexual health	Sexual health
• Surgery	Surgeon; surgery; surgical; operating theatre
• Urology	Urologist; urology
*Note: clinical focus is a proxy variable based on clinical specialty of attendees and/or event description.	
EVENT TYPE	
• Meeting (not otherwise specified)	Search for generic word “meeting”
• Journal club	Journal club; journalclub
• Inservice	Inservice
• Workshop	Workshop
• Grand rounds	Grand round; grandround
• Scientific meeting	scientific meeting; congress; conference AND NOT videoconference/teleconference
• Clinical meeting	internal meeting; departmental meeting; clinical meeting; case review, case conference; case study meeting; case study conference
• Multidisciplinary meeting	Multidisciplinary meeting

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Appendix Table 2:

Coding of three included conditions

Variable name	Keyword search
DEPRESSION	Depress; Anx; Citalopram; Sertraline; Agomelatine; Vortioxetine; Amitriptyline; Clomipramine; Desvenlafaxine; Dothiepin; Doxepin; Duloxetine; Escitalopram; Fluoxetine; Fluvoxamine; Imipramine; Miaserin; Mirtazapine; Moclobemide; Paroxetine; Reboxetine; Tranylcypromine; Trimipramine; Venlafaxine; Brintellix; Valdoxan; Cymbalta; Anafranil; Pristiq; Sinequan; Andepra; Prozac; Tolvon; Avanza; Mirtazon; Remero; Edronax; Zoloft; Xydep; Altven; Efexor
OSTEOPOROSIS	osteop; bone health; bone disease; metabolic bone disease; mineral bone disease; bone mineral; mineral bone; bone and calcium; fracture; Bisphosphonate; Denosumab; Zolendronic acid; Cinacalcet; Teriparatide; Alendronic acid; Alendronate; Cholecalciferol; Calcitriol; Calcium chloride; Disodium Pamidronate; Ibandronate; Raloxifene; Risedronate ; Salcatonin; Sodium Clodronate; Strontium ranelate; Tiludronate; Prolia; Forteo; Sensipar; Adronat; Fosamax; Dronalen; Rocaltrol; Risedronate; Aredia; Bondronat; Evifyne; Evista; Miacalcic; Protos; Skelid; Aclasta; Osteovan; Zometa.
OVERACTIVE BLADDER	Incontinence; Overactive AND bladder; Over active AND bladder; Betmiga; Darifenacin; Oxybutynin; Propantheline; Solifenacin; Tolterodine; Mirabegron; Ditropan; Vesicare; Detrusitol

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Appendix Table 3:

Top 5 sponsoring companies in total and per condition

Company	Number of events (% of category)	Number of attendees (% of category)	Total cost of food and beverage ($AUD)	Total cost of functions ($AUD)	Mean total cost per event (SD) (AUD$)	Median total cost per event (IQR) (AUD$)
General	116,845	3,481,750	84,862,791	286,117,928	2,449.70 (SD=15,020)	263 (153-1,195)
AstraZeneca	13,968 (12.0%)	435,686 (12.5%)	12,725,027.09 (15.0%)	31,766,776 (11.1%)	2,274 (SD=10,878)	318 (165-2,261)
Novartis	10,120 (8.7%)	244,069 (7.0%)	6,600,502.76 (7.8%)	27,467,246 (9.6%)	2,714 (SD=16,109)	270 (167-1,154)
MSD	9,142 (7.8%)	214,621 (6.2%)	5,388,246.54 (6.4%)	18,352,116 (6.4%)	2,007 (SD=9,274)	341 (180-1,182)
Roche	7,383 (6.3%)	174,878 (5.0%)	2,891,426.00 (3.4%)	16,625,126 (5.8%)	2,252 (SD=22,101)	186 (129-284)
Pfizer	7,125 (6.1%)	188,439 (5.4%)	3,740,677.35 (4.4%)	18,464,785 (6.5%)	2,591 (SD=21,482)	236 (141-573)
Depression	1,567	41,472	2,441,950	6,259,581	3,995 (SD=15,895)	1,941 (659 – 3,264)
Servier	803 (51.2%)	19,671 (47.4%)	1,497,510 (61.3%)	3,757,665 (60.0%)	4,680 (SD=1,7837)	2,164 (921 - 3,145)
AstraZeneca	361 (23.0%)	9,577 (23.1%)	551,985 (22.6%)	1,269,764 (20.3%)	3,517 (SD =5,306)	1,082 (126-2,045)
Pfizer	251 (16.0%)	5,160 (12.4%)	182,306 (7.5%)	326,255 (5.2%)	1,300 (SD=1,846)	420 (195-1,978)
Eli Lily	57 (3.6%)	1,175 (2.8%)	28,902 (1.2%)	47,485 (0.8%)	833 (SD=1,591)	165 (75-950)
Janssen	33 (2.1%)	974 (2.35%)	5,760 (0.24%)	56,953 (0.91%)	1,726 (SD=5,788)	187 (106-273)
Osteoporosis	1,375	33,916	2,314,319	6,073,333	4,417 (SD=21,611)	686 (217-2,500)
Amgen	431 (31.4%)	10,120 (29.84%)	943,254 (40.8%)	2,114,304 (34.8%)	4,906 (SD=29,502)	259 (175-630)
Novartis	274 (19.9%)	5,735 (16.91%)	308,064 (13.3%)	971,212 (16.0%)	3,545 (SD=16,701)	369 (159-2,011)
GSK	249 (18.1%)	5,273 (15.55%)	474,364 (20.5%)	928,803 (15.3%)	3,730 (SD=11,982)	2,354 (1,500-3,532)
Servier	206 (15.0%)	4,344 (12.81%)	283,954.11 (12.3%)	523,699.04 (8.6%)	2,542 (SD=6,636)	1,647 (546-2,939)

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Company	Number of events (% of category)	Number of attendees (% of category)	Total cost of food and beverage ($AUD)	Total cost of functions ($AUD)	Mean total cost per event (SD) (AUD$)	Median total cost per event (IQR) (AUD$)
Sanofi	119 (8.7%)	3,798 (11.20%)	100,970.91 (4.4%)	190,200.21 (3.1%)	1,598 (SD=3,205)	440 (120-1,755)
Overactive bladder	190	21,270	467,096	1,136,665	5,951 (SD=41,070)	2,024 (773-3,379)
Astellas	77 (40.5%)	2,294 (10.8%)	113,572 (24.3%)	209,663.47 (18.5%)	2,723 (SD=2,616)	2,277 (1,568-2,956)
CSL	76 (40.0%)	1,950 (9.2%)	94,902 (20.3%)	181,431 (16.0%)	2,387 (SD=2,399)	1,664.50 (169-3,579)
AstraZeneca	9 (4.7%)	194 (0.9%)	3,802 (0.8%)	11,911 (1.0%)	1,323 (SD=883)	795.07 (795-1,778)
Allergan	6 (3.2%)	681 (3.2%)	14,068 (3.0%)	54,569 (4.8%)	9,095 (SD=6,445)	10,654 (1,389-15,148)
Bristol-Myers Squibb	6 (3.2%)	2,710 (12.7%)	900 (0.2%)	66,400 (5.8%)	11,067 (SD=7,645)	16,000 (1,350-16,000)

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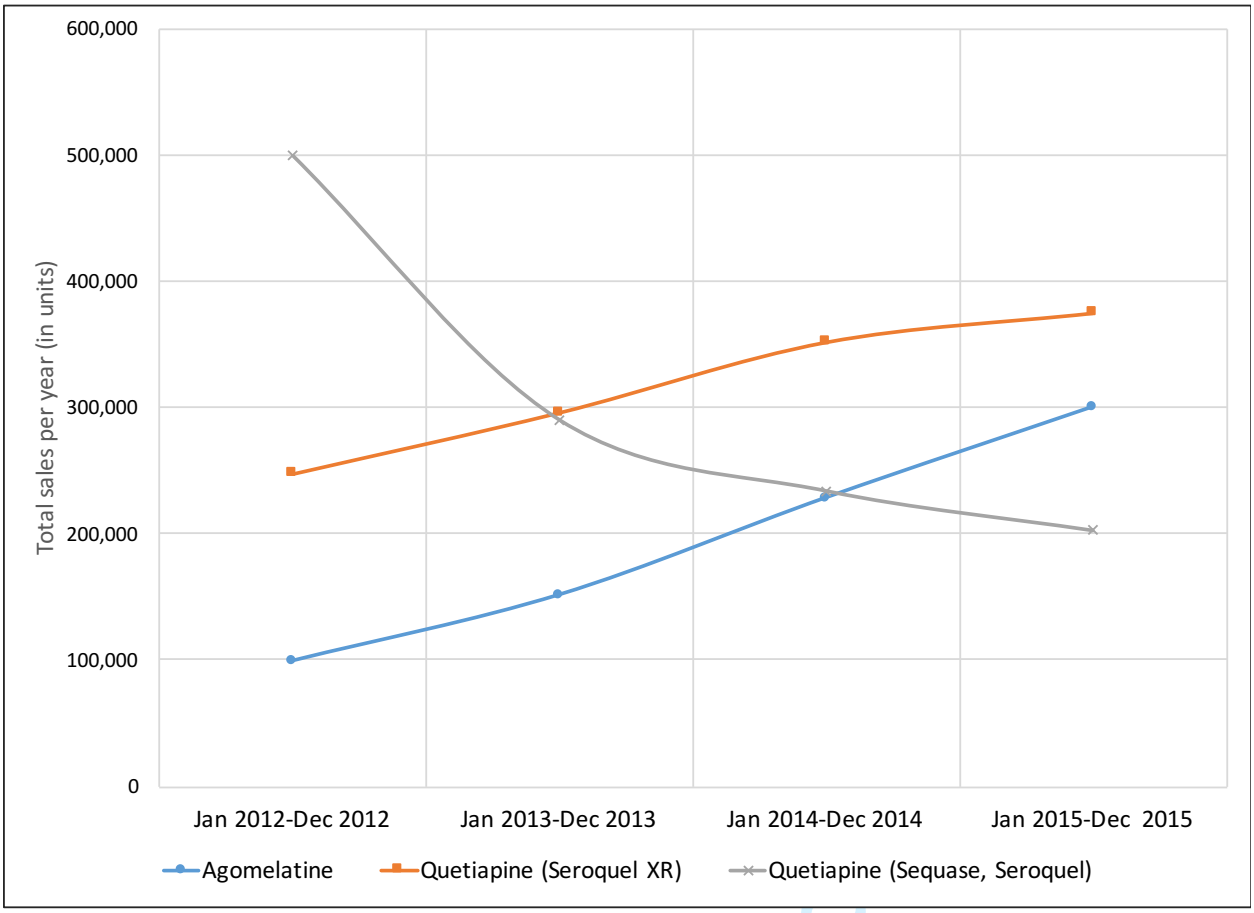
On-line Appendix Figure 3.1

Annual sales of agomelatine, quetiapine for depression (Seroquel XR) and other formulations of quetiapine (Sequase, Seroquel)



Agomelatine: 1 unit = 28 days@ 25mg/day; quetiapine (Seroquel XR, Sequase, Seroquel): 1 unit = 60 days (various doses) Source: IMS Quintiles

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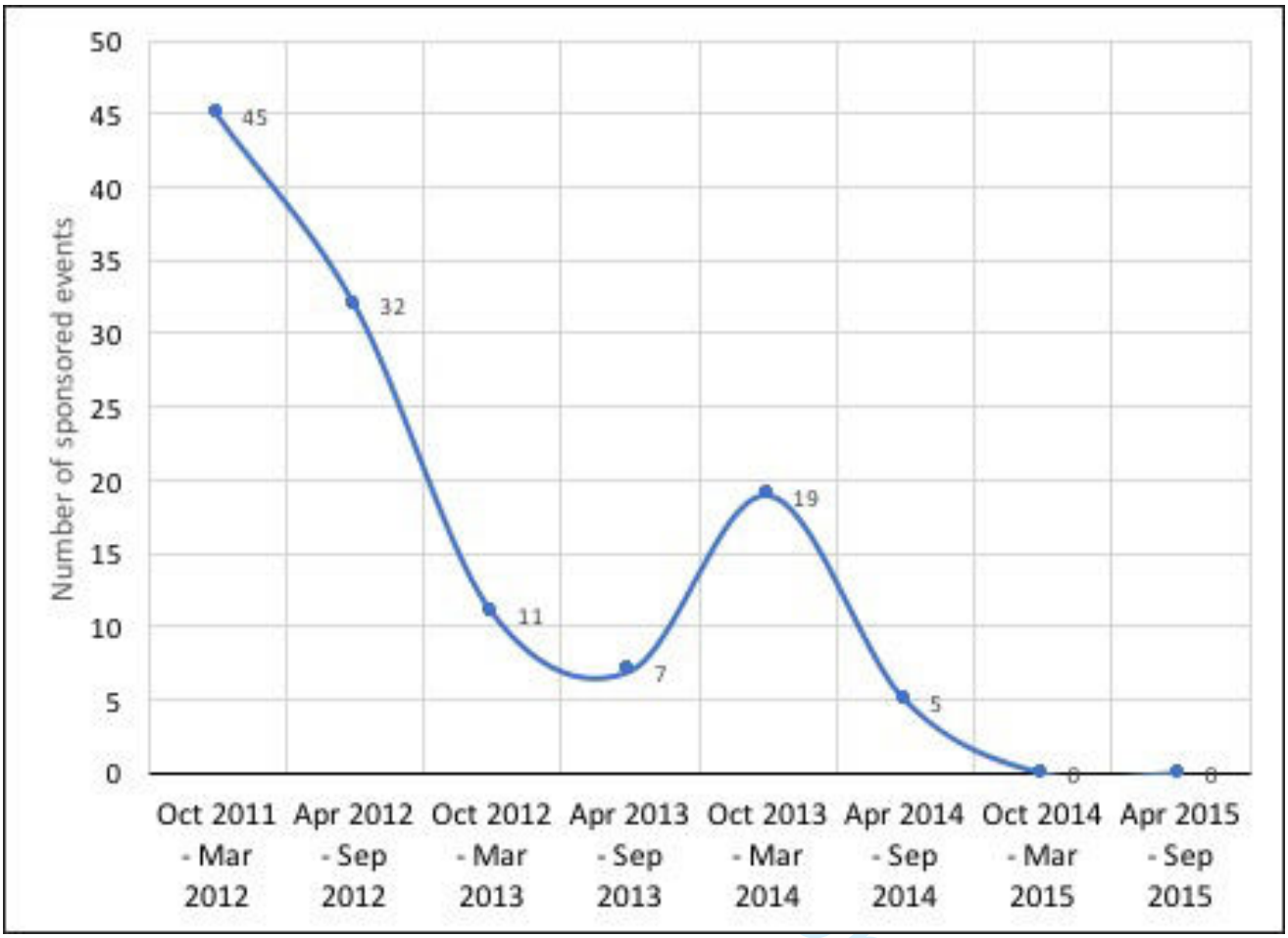
On-line Appendix Figure 3.2

Osteoporosis-related events sponsored by Sanofi



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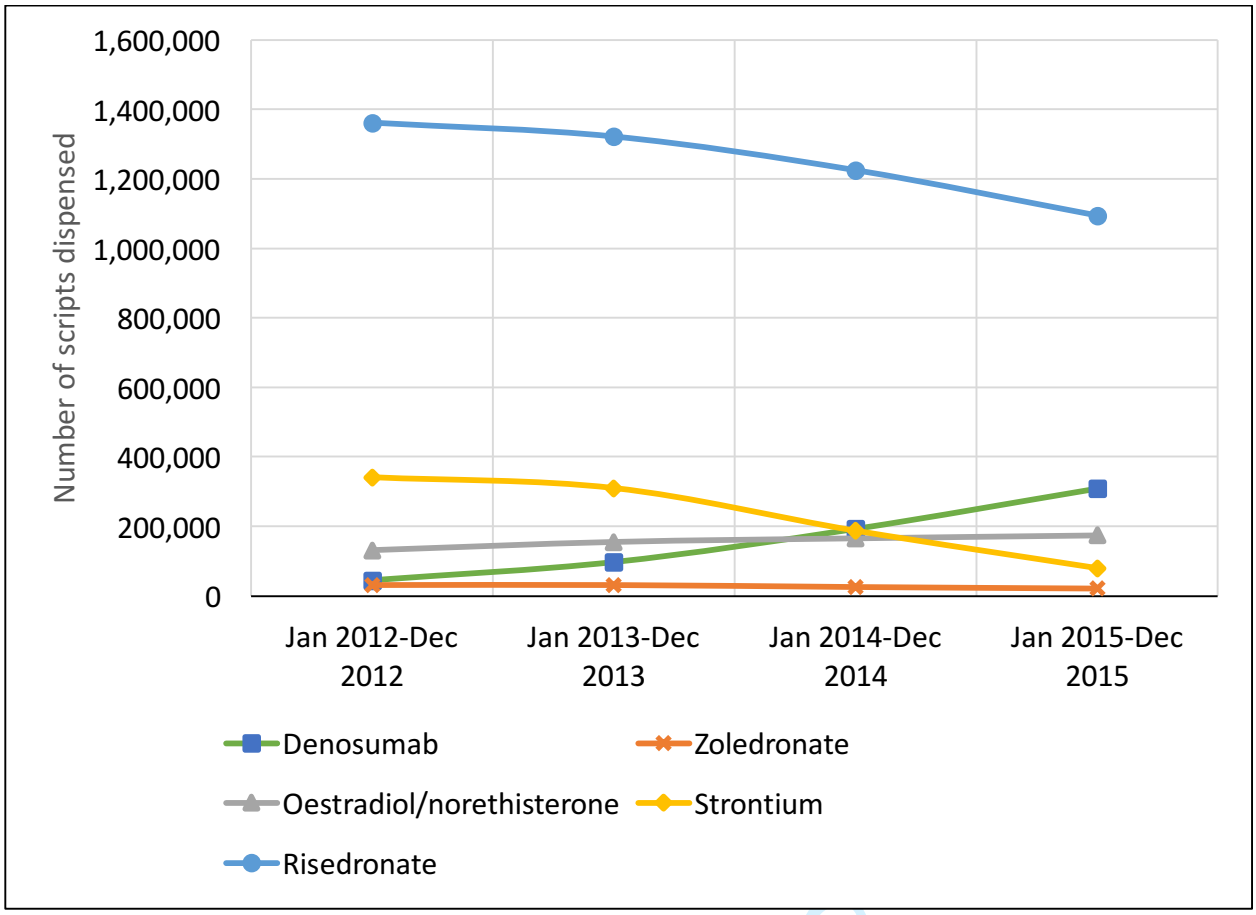
On-line Appendix Figure 3.3

Number of scripts dispensed for osteoporosis drugs, Pharmaceutical Benefits Scheme (PBS)



Source: Australian Statistics on Medicines 2012 to 2015. Available at: https://www.pbs.gov.au/info/browse/statistics#ASM

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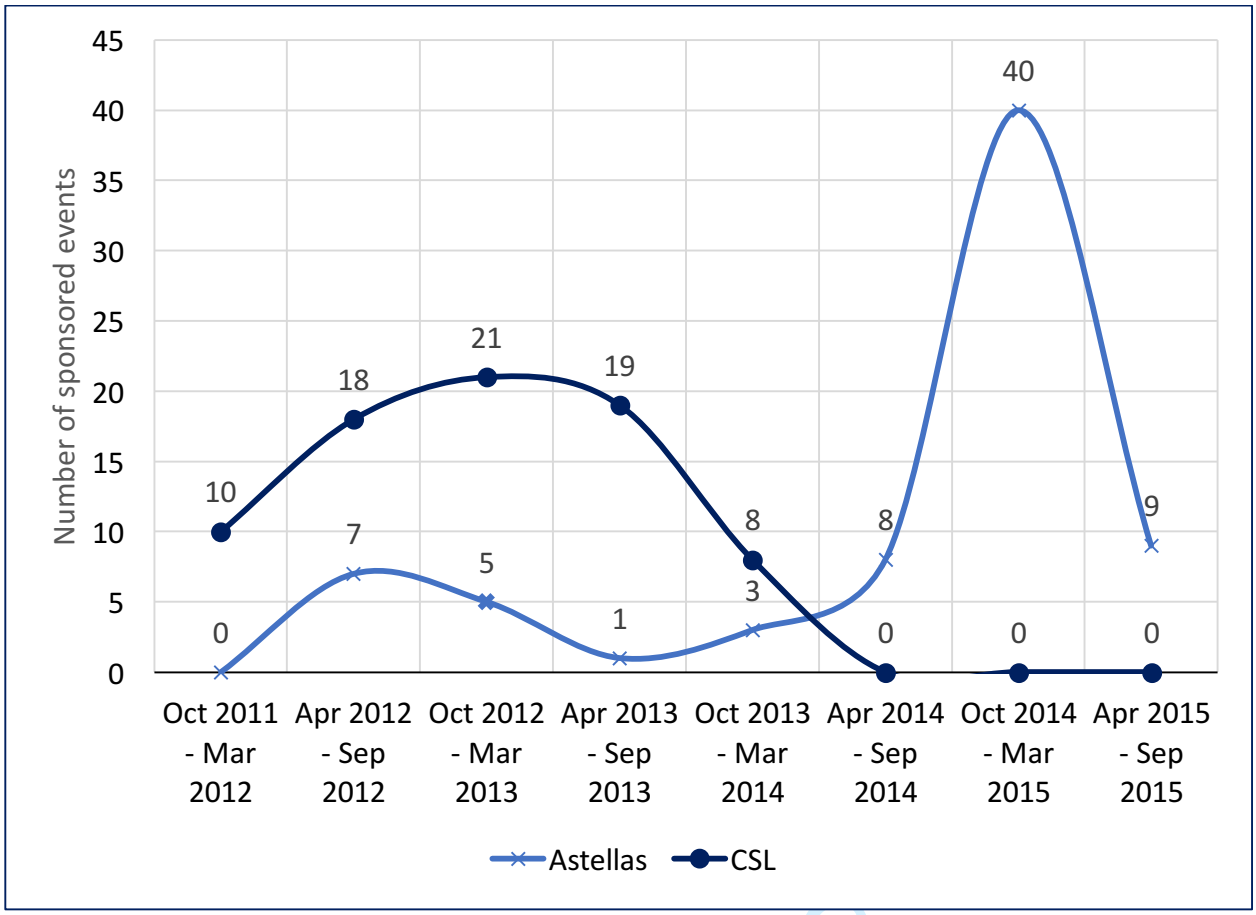
On-line Appendix Figure 3.4

Event sponsorship over the study period by lead overactive bladder sponsors



Note: CSL marketed solifenacin in Australia from February 2011 to October 2014, when marketing rights shifted to Astellas. Astellas also markets mirabegron, approved in Australia in February 2014.

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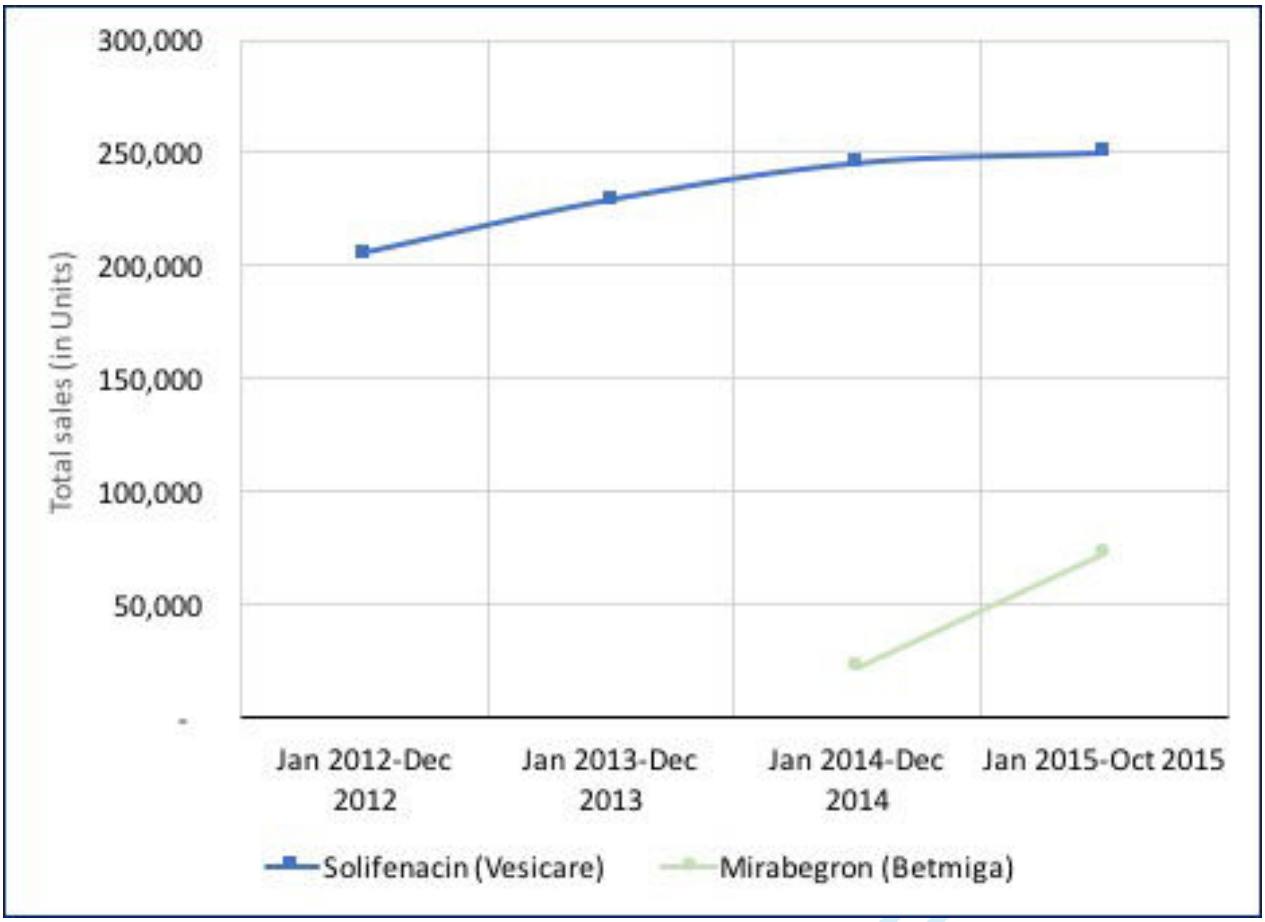
On-line Appendix Figure 3.5

Sales of non-PBS funded overactive bladder drugs over the study period



Mirabegron: 1 unit =30 days@ 25mg/day; solifenacin: 30 days@ 5mg or 10mg/day. Source: IMS Quintiles

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5-7
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 7-9 on-line appendix table 1 ^2
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7-8 (drug data); On-line tables 1 & 2 (event codes)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-8 (drug data); On-line appendix tables 1 & 2 (event codes)
Bias	9	Describe any efforts to address potential sources of bias	Page 9: coder was blinded to sponsor, attendees and event characteristics.
Study size	10	Explain how the study size was arrived at	N/A Population-based
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7-9. Quantitative variables were based on coding above.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	N/A

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		confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Pages 10-12 and on-line appendix
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 10-12 and on-line appendix
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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