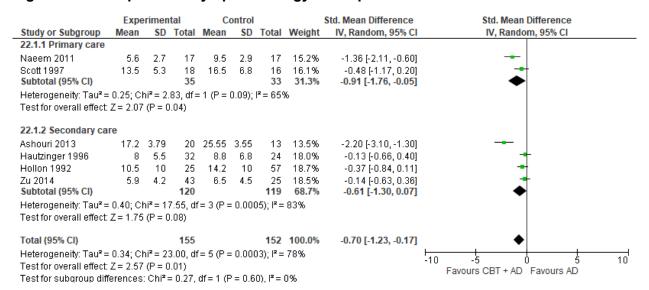
Forest plots for review question 1.2 For adults with depression, what are the relative benefits and harms associated with different settings for the delivery of care?

### Comparison 1. Primary care versus secondary care

Primary care versus secondary care subgroup analysis for Comparison 1a Cognitive and cognitive behavioural therapies individual + antidepressant versus antidepressant

Figure 51: Depression symptomatology at endpoint



# Primary care versus secondary care subgroup analysis for Comparison 1b. Selective serotonin reuptake inhibitors (SSRIs) versus placebo

Figure 52: Depression symptomatology at endpoint

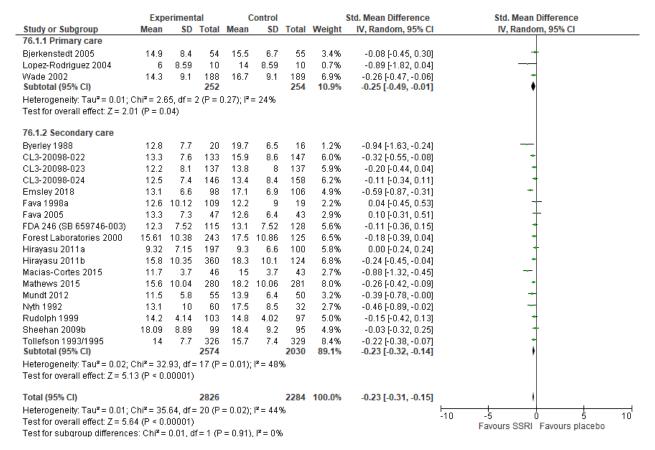


Figure 53: Depression symptomatology change score

| Study or Subgroup  | Mean          | xperimental<br>SD | Total      | Mean         | Control<br>SD     | Total     | Weight       | Std. Mean Difference<br>IV, Random, 95% CI | Std. Mean Difference<br>IV, Random, 95% CI |
|--|---------------|-------------------|------------|--------------|-------------------|-----------|--------------|--|--|
| 6.2.1 Primary care   |               |                   |            |              |                   |           |              | ,,,  | ,,   |
| 3jerkenstedt 2005  | -8.9          | 8                 | 54         | -9.7         | 7                 | 55        | 1.5%         | 0.11 [-0.27, 0.48]                         | +  |
| Nade 2002  | -14.9         | 6.56658206        | 188        | -12          | 6.78196137        | 189       | 2.4%         | -0.43 [-0.64, -0.23]                       | ~  |
| Subtotal (95% CI)  |               |                   | 242        |              |                   | 244       | 3.9%         | -0.19 [-0.71, 0.34]                        | •  |
| Heterogeneity: Tau² = 0.12; Chi² = 6.11, df = 1 (P = 0<br>Test for overall effect: Z = 0.70 (P = 0.48)                         | .01); I² = 8  | 4%                |            |              |                   |           |              |  |  |
| 6.2.2 Secondary care   |               |                   |            |              |                   |           |              |  |  |
| 9060 07 001  | -13.08        | 10.2191           |            | -10.91       | 9.386048          | 11        | 0.5%         | -0.21 [-1.03, 0.61]                        |  |
| ndreoli 2002/Dubini 1997/Massana 1998_study 1  | -13.3         | 4.6               | 127        | -8.6         | 4.47              | 128       | 2.1%         | -1.03 [-1.29, -0.77]                       | ~  |
| aune 2018  | -15.96        | 8.58              | 52         | -8           | 8.38              | 48        | 1.4%         | -0.93 [-1.34, -0.52]                       | -  |
| innemann 2008  | -13.42        | 7.61              | 30         | -10.18       | 7.57              | 31        | 1.1%         | -0.42 [-0.93, 0.09]                        | 7  |
| lose 2008  | -12.1         | 10.22             | 129        | -10.6        | 10.42             | 134       | 2.2%         | -0.14 [-0.39, 0.10]                        | 7  |
| urke 2002  | -12.9         | 9.25              | 366        | -9.4         | 9.82              | 119       | 2.4%         | -0.37 [-0.58, -0.16]                       | 7  |
| laghorn 1992a  | -10.72        | 9.39              | 32         | -4.59        | 9.35              | 27        | 1.0%         | -0.65 [-1.17, -0.12]                       |  |
| laghorn 1992b  | -11.44        | 8.32              | 32         | -5.49        | 8.31              | 27        | 1.0%         | -0.71 [-1.23, -0.18]                       | <del>-</del>                               |
| layton 2006_study 1  | -14.2         | 8.07              | 133        | -12.1        | 7.98              | 130       | 2.2%         | -0.26 [-0.50, -0.02]                       | ٦  |
| layton 2006_study 2  | -12.9         | 8.07              | 133        | -11.9        | 7.86              | 126       | 2.2%         | -0.13 [-0.37, 0.12]                        | 1  |
| etke 2004  | -11.7         | 4.61              | 85         | -8.8         | 4.82              | 93        | 1.9%         | -0.61 [-0.91, -0.31]                       | ~  |
| ube 2010   | -15           | 8.82              | 54         | -13          | 8.84              | 122       | 1.8%         | -0.23 [-0.55, 0.10]                        | 7  |
| li Lilly HMAT-A  | -7.4          | 6.44              | 87         | -4.78        | 6.42              | 89        | 1.9%         | -0.41 [-0.70, -0.11]                       | 7  |
| msley 2018   | -13.6         |                   | 98         | -9.5         | 4.82804308        | 106       | 1.9%         | -0.86 [-1.14, -0.57]                       | <u>,</u> 7                                 |
| abre 1992  | -9.13         | 8.14              | 38         | -3.06        | 8.1               | 36        | 1.2%         | -0.74 [-1.21, -0.27]                       | _  |
| abre 1995a   | -9.89         | 8.57              | 261        | -7.6         | 7.5               | 86        | 2.2%         | -0.27 [-0.52, -0.03]                       | 1  |
| ava 1998a  | -10.95        | 9.41              | 109        | -11.6        | 8.9               | 19        | 1.1%         | 0.07 [-0.42, 0.56]                         | I  |
| ava 2005   | -6.3          |                   | 47         | -7.3         | 4.6400431         | 43        | 1.4%         | 0.20 [-0.22, 0.61]                         | T  |
| DA 245 (EMD 68 843-010)  | -11.1         | 7.67              | 92         | -10.2        | 7.96              | 99        | 2.0%         | -0.11 [-0.40, 0.17]                        | J  |
| orest Laboratories 2000  | -12.95        | 9.89              | 243        | -11.2        | 10.35             | 125       | 2.3%         | -0.17 [-0.39, 0.04]                        | 7  |
| orest Research Institute 2005  | -16.26        | 10.37             | 266        | -12.4        | 10.34             | 132       | 2.4%         | -0.37 [-0.58, -0.16]                       |  |
| olden 2002_448   | -11.89        | 8.19              | 206        | -9.9         | 8.04              | 101       | 2.2%         | -0.24 [-0.48, -0.00]                       | 7  |
| olden 2002_449   | -12.69        | 8.2               | 218        | -10.2        | 8.18              | 110       | 2.3%         | -0.30 [-0.53, -0.07]                       |  |
| liguchi 2009   | -9.4          | 6.9               | 148        | -8.3         | 5.8               | 145       | 2.3%         | -0.17 [-0.40, 0.06]                        |  |
| efferson 2000  | -14.7         | 10.56             | 296        | -12.1        | 11.05             | 101       | 2.3%         | -0.24 [-0.47, -0.02]                       | _]   |
| (asper 2012  | -19<br>-17 25 | 10.61<br>8.05     | 139<br>161 | -13.4<br>-14 | 9.27<br>8.87      | 71<br>154 | 1.9%<br>2.3% | -0.55 [-0.84, -0.26]                       |  |
| (eller 2006_Study 062  |               |                   |            |              |                   |           |              | -0.38 [-0.61, -0.16]                       | 1  |
| (ranzler 2006_Group A  | -10.8         | 6.5               | 89<br>31   | -9.6         | 7.8               | 100       | 1.9%         | -0.17 [-0.45, 0.12]                        | 1  |
| am 2016  | -8.8<br>-8.9  | 9.9<br>2.45051015 | 46         | -6.5<br>-5.7 | 9.6<br>2.46880538 | 43        | 1.1%         | -0.23 [-0.74, 0.27]                        | _ 1  |
| facias-Cortes 2015<br>fathews 2015   | -8.9<br>-15.9 | 10.04             | 280        | -13.6        | 10.06             | 281       | 2.6%         | -1.29 [-1.75, -0.83]                       | - ]  |
| Miller 1989a   | -15.9         | 5.9               | 19         | -6.2         | 7.2               | 201       | 0.8%         | -0.23 [-0.39, -0.06]<br>0.03 [-0.58, 0.64] |  |
| Montgomery 1992  | -12.36        | 8.81              | 129        | -10.56       | 7.76              | 64        | 1.9%         | -0.21 [-0.51, 0.09]                        |  |
| fundt 2012   | -13.4         | 5.7               | 55         | -10.30       | 6.6               | 50        | 1.5%         | -0.44 [-0.82, -0.05]                       | 4  |
| //////////////////////////////////////   | -10.23        | 7.67              | 120        | -8.25        | 7.56              | 123       | 2.1%         | -0.26 [-0.51, -0.01]                       | <u>_</u>                                   |
| 1Y-1045/BRL-029060/1 (PAR 128)   | -12.39        | 8.77              | 694        | -9           | 8.63              | 136       | 2.5%         | -0.39 [-0.57, -0.20]                       | _  |
| lierenberg 2007  | -7.23         | 6.62              | 274        | -5.97        | 6.79              | 137       | 2.4%         | -0.19 [-0.39, 0.02]                        | J  |
| IKD20006 (NCT00048204)   | -11.1         | 7.9               | 117        | -10.9        | 7.8               | 118       | 2.1%         | -0.03 [-0.28, 0.23]                        | <b></b>                                    |
| lyth 1992  | -13.1         |                   | 60         | -6.7         |                   | 32        | 1.2%         | -0.95 [-1.40, -0.49]                       |  |
| AR 01 001 (GSK & FDA)  | -13.36        | 7.93              | 22         | -11.33       | 7.93              | 21        | 0.8%         | -0.25 [-0.85, 0.35]                        | <del>-</del>                               |
| apaport 2009   | -12.11        | 8.02              | 173        | -8.85        | 8                 | 178       | 2.4%         | -0.41 [-0.62, -0.19]                       | -  |
| Reimherr 1990  | -11.66        | 8.24              | 142        | -8.16        | 7.85              | 141       | 2.2%         | -0.43 [-0.67, -0.20]                       | -  |
| ER 315 (FDA)   | -8.9          | 4.52              | 76         | -7.8         | 8                 | 73        | 1.8%         | -0.17 [-0.49, 0.15]                        | 4  |
| heehan 2009b   | -11.42        |                   | 99         | -11.02       | 6.86603233        | 95        | 2.0%         | -0.06 [-0.34, 0.22]                        | 4  |
| tark 1985  | -11           | 10.1              | 185        | -8.2         | 9                 | 169       | 2.4%         | -0.29 [-0.50, -0.08]                       | -  |
| tudy 62b (FDA)   | -8.82         | 8.71              | 297        | -5.69        | 8.65              | 48        | 1.8%         | -0.36 [-0.66, -0.05]                       | 4  |
| tudy F1J-MC-HMAQ - Study Group B   | -7.63         | 7                 | 37         | -7.1         | 6.96              | 72        | 1.4%         | -0.08 [-0.47, 0.32]                        | +  |
| ollefson 1993/1995   | -8.1          | 7.6               | 326        | -6.4         | 7.1               | 329       | 2.7%         | -0.23 [-0.38, -0.08]                       | -  |
| EN XR 367 (FDA)  | -11.26        | 10.55             | 80         | -13.1        | 10.63             | 81        | 1.8%         | 0.17 [-0.14, 0.48]                         | +  |
| /ELL AK1A4006  | -13.9         | 10.87             | 146        | -12.2        | 9.73              | 148       | 2.3%         | -0.16 [-0.39, 0.06]                        | 4  |
| Vernicke 1987  | -8.83         | 8.67              | 297        | -5.7         | 8.6               | 48        | 1.8%         | -0.36 [-0.67, -0.05]                       | 4  |
| Vernicke 1988  | -10.6         | 8.3               | 183        | -7           | 8.6               | 77        | 2.0%         | -0.43 [-0.70, -0.16]                       | -  |
| ubtotal (95% CI)   |               |                   | 7571       |              |                   | 5029      | 96.1%        | -0.33 [-0.39, -0.26]                       | - 1  |
| Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 140.90, df = 51 (Piest for overall effect: $Z = 9.74$ (P < 0.00001) | < 0.0000      | 1); I²= 64%       |            |              |                   |           |              |  |  |
| otal (95% CI)  |               |                   | 7813       |              |                   | 5273      | 100.0%       | -0.32 [-0.39, -0.26]                       |  |
| leterogeneity: Tau <sup>z</sup> = 0.03; Chi <sup>z</sup> = 147.01, df = 53 (P  | < 0.0000      | 1); I² = 64%      |            |              |                   |           |              |  | 10 5                                       |
| est for overall effect: Z = 9.82 (P < 0.00001)   |               |                   |            |              |                   |           |              |  | -10 -5 0 5                                 |
|  |               |                   |            |              |                   |           |              |  | Favours SSRI Favours placebo               |

Figure 54: Response

| organ 1994 epola 2003 file (ade 2002 ubtotal (95% CI) otal events est for overall effect: Z = 3.25 (P = 0.001)  6.4.2 Secondary care endreoil 2002/Dubini 1997/Massana 1998_study 1 innemann 2008 ose 2008 urke 2002 yerley 1988 L3-20098-022 L3-2098-024 laghorn 1992b layton 2006_study 1 layton 2006_study 2 erke 2004 urbe 2010 umbar 1993 li Lilly HMAT-A msley 2018 abay 1998a orest Laboratories 2000 orest Research Institute 2005 oldstein 2004 ual 2003 lirayasu 2011a lirayasu 2011a lirayasu 2011b efferson 2000 dasper 2012 at 2004 ramer 1998 ramer 1999 undt 2012 http://dx.com/dx.c | 3<br>6<br>6<br>0<br>7<br>9<br>9<br>9<br>4<br>4<br>7<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9<br>9   | 57<br>99<br>315<br>191<br>662<br>127<br>43<br>132<br>379<br>32<br>137<br>148<br>32<br>170<br>89<br>278<br>109<br>278<br>109<br>274<br>33<br>87<br>44<br>148<br>205<br>361<br>310<br>140<br>28<br>311<br>310<br>310<br>311<br>310<br>310<br>310<br>310<br>310<br>310  | 21<br>40<br>74<br>79<br>214<br>43<br>17<br>51<br>33<br>34<br>4<br>49<br>91<br>66<br>69<br>30<br>22<br>4<br>43<br>31<br>55<br>56<br>66<br>66<br>63<br>32<br>15<br>56<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66 | 128 39 135 127 29 149 158 39 135 70 107 107 108 108 107 108 108 107 108 108 108 108 108 108 108 108 108 108  | 0.8% 1.6% 2.8% 2.5% 7.7%  1.8% 1.0% 1.8% 1.6% 0.2% 2.3% 2.3% 2.3% 2.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1  | 0.97 [0.59, 1.58] 1.28 [0.94, 1.74] 1.21 [1.00, 1.46] 1.29 [1.04, 1.60] 1.23 [1.09, 1.39] 1.69 [1.27, 2.25] 1.33 [0.86, 2.07] 1.18 [0.89, 1.58] 1.82 [1.33, 2.48] 3.17 [1.18, 8.55] 1.21 [0.97, 1.52] 1.04 [0.87, 1.26] 2.50 [1.09, 5.71] 1.30 [1.05, 1.60] 1.18 [0.94, 1.48] 1.69 [1.30, 2.19] 1.09 [0.79, 1.52] 2.41 [1.67, 3.49] 1.60 [1.05, 2.43] 1.61 [1.05, 1.60] 1.18 [0.90, 1.73] 1.10 [0.70, 1.73] 1.10 [0.70, 1.73] 1.10 [0.70, 1.73] 1.10 [0.70, 1.73] 1.10 [0.70, 1.73] 1.10 [0.70, 1.73] 1.11 [0.90, 1.49] 1.12 [0.67, 1.89] 1.37 [1.06, 1.78] 1.03 [0.86, 1.23] 1.37 [1.06, 1.78] 1.03 [0.86, 1.23] 1.37 [1.06, 1.78] 1.03 [0.86, 1.23] 1.37 [1.06, 1.78] 1.03 [0.86, 1.23] 1.41 [1.21, 1.94] 1.64 [0.71, 3.78] 1.60 [1.03, 2.51] 1.43 [0.93, 2.19] 0.87 [0.41, 1.84] 3.55 [1.45, 8.68] 1.24 [1.07, 1.44] |   |
|--|--|--|---|--|---|---|---|
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| /ade 2002 ubtotal (95% CI) otal events   sterogeneity: Tau*= 0.00; Chi*= 1.18, df = 3 (P = 0.76); P*= est for overall effect: Z = 3.25 (P = 0.001)   6.4.2 Secondary care   ndreoil 2002/Dubini 1997/Massana 1998_study 1   innemann 2008   sterogeneity   see 2008   sterogeneity   see 2008   sterogeneity   see 2008   sterogeneity   see 2002   sterogeneity   see 2002   sterogeneity   see 2004   sterogeneity   sterogeneity   sterogeneity   sterogeneity   sterogeneity   sterogeneity   see 2004   sterogeneity   sterogen | 3<br>6<br>6<br>0<br>7<br>2<br>5<br>9<br>9<br>9<br>4<br>4<br>7<br>7<br>9<br>9<br>5<br>5<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | 191<br>662<br>127<br>43<br>132<br>379<br>32<br>148<br>36<br>142<br>149<br>86<br>62<br>170<br>89<br>99<br>257<br>44<br>44<br>205<br>33<br>87<br>44<br>148<br>205<br>33<br>10<br>140<br>28<br>89<br>27<br>44<br>44<br>46<br>46<br>47<br>47<br>48<br>48<br>48<br>48<br>48<br>48<br>48<br>48<br>48<br>48<br>48<br>48<br>48 | 79<br>214<br>43<br>177<br>511<br>33<br>4<br>99<br>91<br>6<br>6<br>6<br>99<br>14<br>30<br>22<br>4<br>30<br>22<br>10<br>51<br>55<br>66<br>66<br>69<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66                                | 128<br>399<br>135<br>127<br>29<br>149<br>158<br>36<br>141<br>1137<br>90<br>107<br>70<br>89<br>3135<br>70<br>89<br>146<br>105<br>124<br>105<br>105<br>107<br>100<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>3   | 1.8%<br>1.0%<br>1.8%<br>1.6%<br>0.2%<br>2.8%<br>0.3%<br>2.5%<br>2.0%<br>1.5%<br>2.13%<br>2.14%<br>2.14%<br>2.14%<br>2.14%<br>2.14%<br>2.14%<br>2.18%<br>1.19%<br>0.8%<br>2.18%<br>1.19%<br>0.8%<br>1.19%<br>0.8%<br>1.19%<br>0.9%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2.19%<br>2. | 1.29 [1.04, 1.60] 1.23 [1.09, 1.39] 1.69 [1.27, 2.25] 1.33 [0.86, 2.07] 1.18 [0.89, 1.58] 1.82 [1.33, 2.48] 3.17 [1.18, 8.55] 1.21 [0.97, 1.52] 1.04 [0.87, 1.26] 2.50 [1.09, 5.71] 1.30 [1.05, 1.60] 1.18 [0.94, 1.48] 1.69 [1.30, 2.19] 1.09 [0.79, 1.52] 2.41 [1.67, 3.49] 1.60 [1.05, 2.43] 1.62 [1.18, 2.24] 1.31 [0.96, 1.78] 1.10 [0.70, 1.73] 1.16 [0.90, 1.48] 1.31 [0.90, 1.78] 1.43 [1.14, 1.78] 1.09 [0.72, 1.65] 1.29 [0.86, 1.94] 1.12 [0.67, 1.89] 1.37 [1.06, 1.76] 1.36 [1.02, 1.82] 1.48 [1.12, 1.94] 1.64 [0.71, 3.78] 1.60 [1.03, 2.51] 1.43 [0.93, 2.19] 0.87 [0.41, 1.84] 0.87 [0.41, 1.84] 0.87 [0.41, 1.84] 0.87 [0.41, 1.84]   |   |
| ubtotal (95% CI)  total events  stetrogeneity. Tau* = 0.00; Chi* = 1.18, df = 3 (P = 0.76); P* = est for overall effect: Z = 3.25 (P = 0.001)  6.4.2 Secondary care  ndreoli 2002/Dubini 1997/Massana 1998_study 1 innemann 2008  sse 2008  urke 2002  yerley 1988  L3-20098-024  laghorn 1992b  layton 2006_study 1  layton 2006_study 2  telke 2004  uibe 2010  uinbar 1993  ii Lilly HMAT-A  msley 2018  abre 1995a  ava 1998a  orest Laboratories 2000  orest Research Institute 2005  oldstein 2004  ual 2003  iguchi 2009  ilrayasu 2011a  irayasu 2011a  irayasu 2011b  efferson 2000  asper 2012  at 2004  ramer 1998  ramzer 1998  ramzer 2006_Group A  am 2016  aciass-Cortes 2015  isthews 2015  lendels 1999  undt 2012  yth 1982-1990  irerenberg 2007  KD20006 (NCT00048204)  yth 1992  litel 1997  AR 01 001 (GSK & FDA)  erahia 2006  esselow 1989a  esselow 1989a  esselow 1989b  lapaport 2009  atti 2011_study 096  awindran 1996  einher 1990  | 660%<br>25599944<br>77955002444998833333399966   | 127<br>43<br>132<br>137<br>32<br>137<br>132<br>137<br>148<br>36<br>142<br>86<br>62<br>170<br>89<br>99<br>257<br>274<br>44<br>205<br>331<br>140<br>28<br>28<br>31<br>140<br>28<br>31<br>440<br>440<br>440<br>440<br>440<br>440<br>440<br>440<br>440<br>44   | 214<br>43<br>177<br>513<br>33<br>4<br>66<br>99<br>91<br>66<br>44<br>41<br>59<br>30<br>20<br>24<br>43<br>66<br>32<br>27<br>7<br>15<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66<br>66                             | 128<br>39<br>135<br>127<br>29<br>149<br>158<br>36<br>141<br>133<br>138<br>171<br>19<br>129<br>135<br>70<br>89<br>39<br>39<br>146<br>105<br>124<br>105<br>124<br>105<br>124<br>105<br>106<br>107<br>107<br>108<br>108<br>108<br>108<br>108<br>108<br>108<br>108<br>108<br>108                                   | 1.8% 1.0% 1.8% 1.0% 2.3% 2.3% 2.5% 2.3% 2.5% 1.3% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1   | 1.23 [1.09, 1.39]  1.69 [1.27, 2.25] 1.33 [0.86, 2.07] 1.18 [0.89, 1.58] 1.82 [1.33, 2.48] 3.17 [1.18, 8.55] 1.21 [0.97, 1.52] 1.04 [0.87, 1.26] 2.50 [1.09, 5.71] 1.30 [1.05, 1.60] 1.18 [0.94, 1.48] 1.69 [1.30, 2.19] 1.09 [0.79, 1.52] 2.41 [1.67, 3.49] 1.60 [1.05, 2.43] 1.60 [1.18, 2.24] 1.31 [0.96, 1.78] 1.10 [0.70, 1.73] 1.16 [0.90, 1.48] 1.43 [1.14, 1.78] 1.09 [0.72, 1.65] 1.29 [0.86, 1.94] 1.12 [0.67, 1.89] 1.37 [1.06, 1.76] 1.36 [1.02, 1.82] 1.48 [1.12, 1.94] 1.64 [0.71, 3.78] 1.60 [1.03, 2.51] 1.43 [0.93, 2.19] 0.87 [0.41, 1.84] 3.55 [1.45, 8.68]  |   |
| otal events  ieterogeneity: Tau* = 0.00; Chi* = 1.18, df = 3 (P = 0.76); P* = est for overall effect: Z = 3.25 (P = 0.001)  6.4.2 Secondary care  ndreoli 2002/Dubini 1997/Massana 1998_study 1  innemann 2008  ose 2008  urke 2002  urke 2002  12  yerley 1988  L3-20098-024  L3-20098-024  L3ayton 2006_study 1  layton 2006_study 2  etke 2004  urbe 2010  unbar 1993  ii Lilly HMAT-A  msley 2018  abre 1995a  ava 1998a  orest Laboratories 2000  orest Research Institute 2005  oldstein 2004  uala 2003  iirayasu 2011a  iirayasu 2011a  iirayasu 2011b  efferson 2000  asper 2012  atz 2004  ramer 1998  ranzler 2006_Group A  am 2016  lacias-Cortes 2015  athews 2015  endels 1999  undt 2012  Y-1042/BRL-029060/CPMS-251  Y-1045/BRL-029060/CPMS-251  Y-1045/BRL-029060/CPM | 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6  | 127<br>43<br>132<br>379<br>32<br>137<br>148<br>36<br>62<br>170<br>89<br>99<br>278<br>109<br>257<br>43<br>33<br>87<br>44<br>148<br>205<br>310<br>140<br>289<br>31<br>46<br>289  | 43<br>17<br>51<br>33<br>4<br>9<br>91<br>6<br>6<br>99<br>1<br>5<br>9<br>30<br>24<br>4<br>30<br>24<br>30<br>21<br>5<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6                                 | 128<br>39<br>135<br>127<br>29<br>149<br>158<br>36<br>141<br>137<br>90<br>107<br>70<br>89<br>129<br>146<br>105<br>124<br>105<br>70<br>105<br>71<br>25<br>70<br>100<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>3   | 1.8% 1.6% 0.2% 2.3% 2.8% 0.3% 2.5% 2.3% 2.0% 1.5% 1.1% 1.6% 1.7% 0.9% 2.14% 1.1% 1.18% 1.18% 1.19% 0.3% 3.3%  | 1.69 [1.27, 2.25] 1.33 [0.86, 2.07] 1.18 [0.89, 1.58] 1.82 [1.33, 2.48] 3.17 [1.18, 8.55] 1.21 [0.97, 1.52] 1.04 [0.87, 1.26] 2.50 [1.09, 5.71] 1.30 [1.05, 1.60] 1.18 [0.94, 1.48] 1.69 [1.30, 2.19] 1.09 [0.79, 1.52] 2.41 [1.67, 3.49] 1.60 [1.05, 2.43] 1.61 [1.67, 1.49] 1.62 [1.18, 2.24] 1.31 [0.96, 1.78] 1.16 [0.90, 1.49] 1.43 [1.14, 1.78] 1.09 [0.72, 1.65] 1.29 [0.86, 1.94] 1.12 [0.67, 1.89] 1.37 [1.06, 1.76] 1.36 [1.02, 1.82] 1.37 [1.06, 1.76] 1.36 [1.02, 1.82] 1.48 [1.12, 1.94] 1.64 [0.71, 3.78] 1.60 [1.03, 2.51] 1.43 [0.93, 2.19] 0.87 [0.41, 1.84] 0.87 [0.41, 1.84] 0.87 [0.41, 1.84]   |   |
| leterogeneity: Tau*= 0.00; Chi*= 1.18, df = 3 (P = 0.76); P = est for overall effect. Z = 3.25 (P = 0.001)  6.4.2 Secondary care  dreoil 2002/Joubini 1997/Massana 1998_study 1 innemann 2008 ose 2008 urke 2002 yerley 1998 L-3-20098-022 L-3-20098-022 L-3-20098-024 laghorn 1992b laghorn 1992b layton 2006_study 1 layton 2006_study 2 etke 2004 urbe 2010 urbar 1993 ii Lilly HMAT-A msley 2018 abre 1995a ava 1998a orest Laboratories 2000 orest Research Institute 2005 oldstein 2004 usul 2003 iguchi 2009 irayasu 2011a irayasu 2011b efferson 2000 asper 2012 atz 2004 ramer 1998 ranzler 2006_Group A am 2016 lacias-Cortes 2015 athews 2015 endels 1999 undt 2012 YY-1042/BRL-029060/CPMS-251 YY-1045/BRL-029060/f (PAR 128) emeroff 2007 ikD 20006 (NCT00048204) yth 1992 litel 1997 AR 01 001 (GSK & FDA) erarbia 2006 eselow 1989a eselow 1989b einherr 1990 eiti 2011_study 096 eiminerr 1990 eiti 2011_study 096 eiminerr 1990   | 0% 255999 477995002 499288 48833399966   | 43<br>132<br>379<br>32<br>137<br>148<br>36<br>142<br>149<br>86<br>62<br>170<br>89<br>99<br>278<br>109<br>277<br>44<br>148<br>205<br>274<br>33<br>87<br>44<br>140<br>28<br>89<br>31<br>40<br>28<br>89<br>31<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40                               | 43<br>17<br>51<br>33<br>4<br>9<br>91<br>6<br>6<br>99<br>1<br>5<br>9<br>30<br>24<br>4<br>30<br>24<br>30<br>21<br>5<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6<br>6                                 | 39 135 127 29 149 158 36 36 141 137 79 31 138 171 90 135 70 89 39 36 146 105 71 25 70 100 30 30 43 290   | 1.0% 1.8% 1.6% 0.2% 2.3% 2.5% 2.3% 2.5% 1.5% 1.3% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1   | 1.33 [0.86, 2.07] 1.18 [0.89, 1.58] 1.82 [1.33, 2.48] 3.17 [1.18, 8.55] 1.21 [0.97, 1.52] 1.04 [0.87, 1.26] 2.50 [1.09, 57, 1.60] 1.18 [0.94, 1.48] 1.69 [1.30, 2.19] 1.09 [0.79, 1.52] 2.41 [1.67, 3.49] 1.60 [1.05, 2.43] 1.60 [1.18, 2.24] 1.31 [0.96, 1.78] 1.10 [0.70, 1.73] 1.16 [0.90, 1.49] 1.43 [1.14, 1.78] 1.09 [0.72, 1.65] 1.29 [0.86, 1.94] 1.12 [0.67, 1.89] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.07, 1.78] 1.38 [1.09, 1.79] 1.39 [1.09, 1.79] 1.31 [1.09, 1.79] 1.32 [1.09, 1.79] 1.33 [1.09, 1.79] 1.34 [1.09, 1.79] 1.35 [1.09, 1.79] 1.48 [1.12, 1.94] 1.48 [1.12, 1.94] 1.49 [0.71, 3.78] 1.60 [1.03, 2.51] 1.43 [0.93, 2.19] 0.87 [0.41, 1.84] 3.55 [1.45, 8.68]   |   |
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| 6.4.2 Secondary care  ndreoli 2002/Dubini 1997/Massana 1998_study 1 innemann 2008 ose 2008 urke 2002 yerley 1988 L3-20098-022 laghorn 1992b layton 2006_study 1 layton 2006_study 2 etke 2004 urbe 2010 urbar 1993 li Lilly HMAT-A msley 2018 abre 1995a ava 1998a orest Laboratories 2000 orest Research Institute 2005 oldstein 2002 oldstein 2004 ual 2003 lirayasu 2011a lirayasu 2011b efferson 2000 asper 2012 atz 2004 ramer 1998 ranzler 2006_Group A am 2016 acias-Cortes 2015 lathews 2015 lendels 1999 undt 2012 yerley 1988 de 1999 undt 2012 yerley 1988 de 1999 undt 2012 irayley 1988 lendels 1999 undt 2016 lerenberg 2007 KD20006 (NCT00048204) yth 1992 lier 1997 KR 01 001 (GSK & FDA) erahia 2006 esselow 1989a esselow 1989a esselow 1989a esselow 1989b lapaport 2009 atti 2011_study 096 awindran 1996 eimherr 1990   | 55<br>99<br>44<br>77<br>99<br>55<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60   | 43<br>132<br>379<br>32<br>137<br>148<br>36<br>142<br>149<br>86<br>62<br>170<br>89<br>99<br>278<br>109<br>277<br>44<br>148<br>205<br>274<br>33<br>87<br>44<br>140<br>28<br>89<br>31<br>40<br>28<br>89<br>31<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40                               | 177 511 333 44 699 911 699 644 411 559 300 224 32 100 511 566 666 455 366 366 666 455 666 666 666 666 666 666 666 6   | 39 135 127 29 149 158 36 36 141 137 79 31 138 171 90 135 70 89 39 36 146 105 71 25 70 100 30 30 43 290   | 1.0% 1.8% 1.6% 0.2% 2.3% 2.5% 2.3% 2.5% 1.5% 1.3% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1   | 1.33 [0.86, 2.07] 1.18 [0.89, 1.58] 1.82 [1.33, 2.48] 3.17 [1.18, 8.55] 1.21 [0.97, 1.52] 1.04 [0.87, 1.26] 2.50 [1.09, 57, 1.60] 1.18 [0.94, 1.48] 1.69 [1.30, 2.19] 1.09 [0.79, 1.52] 2.41 [1.67, 3.49] 1.60 [1.05, 2.43] 1.60 [1.18, 2.24] 1.31 [0.96, 1.78] 1.10 [0.70, 1.73] 1.16 [0.90, 1.49] 1.43 [1.14, 1.78] 1.09 [0.72, 1.65] 1.29 [0.86, 1.94] 1.12 [0.67, 1.89] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.07, 1.78] 1.38 [1.09, 1.79] 1.39 [1.09, 1.79] 1.31 [1.09, 1.79] 1.32 [1.09, 1.79] 1.33 [1.09, 1.79] 1.34 [1.09, 1.79] 1.35 [1.09, 1.79] 1.48 [1.12, 1.94] 1.48 [1.12, 1.94] 1.49 [0.71, 3.78] 1.60 [1.03, 2.51] 1.43 [0.93, 2.19] 0.87 [0.41, 1.84] 3.55 [1.45, 8.68]   |   |
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| innemann 2008 ose 2008 urke 2002 yerley 1988 L3-20098-022 L3-20098-024 laghorn 1992b layton 2006_study 1 layton 2006_study 2 etke 2004 ube 2010 unbar 1993 li Lilly HMAT-A msley 2018 abre 1995a ava 1998a orest Laboratories 2000 orest Research Institute 2005 oldstein 2004 ual 2003 liiguchi 2009 lirayasu 2011a lirayasu 2011b efferson 2000 asper 2012 atz 2004 ramer 1998 ramzer 1998 arazler 2006_Group A am 2016 acias-Cortes 2015 lendels 1999 undt 2012 Y-1045/BRL-029060/CPMS-251 IY-1045/BRL-029060/I (PAR 128) lemeroff 2007 KD20006 (NCT00048204) yth 1992 lie 1997 KR 01 001 (GSK & FDA) erahia 2006 esselow 1989a esselow 1989a esselow 19898 espaport 2009 atti 2011_study 096 awindran 1995 eimherr 1990 eimherr 1990 atti 2011_study 096 awindran 1995 eimherr 1990 atti 2011_study 096 awindran 1995 eimherr 1990   | 55<br>99<br>44<br>77<br>99<br>50<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60   | 43<br>132<br>379<br>32<br>137<br>148<br>36<br>142<br>149<br>86<br>62<br>170<br>89<br>99<br>278<br>109<br>277<br>44<br>148<br>205<br>274<br>33<br>87<br>44<br>140<br>28<br>89<br>31<br>40<br>28<br>89<br>31<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40                               | 177 511 333 44 699 911 699 644 411 559 300 224 32 100 511 566 666 455 366 366 666 455 666 666 666 666 666 666 666 6   | 39 135 127 29 149 158 36 36 141 137 79 31 138 171 90 135 70 89 39 36 146 105 71 25 70 100 30 30 43 290   | 1.0% 1.8% 1.6% 0.2% 2.3% 2.5% 2.3% 2.5% 1.5% 1.3% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1   | 1.33 [0.86, 2.07] 1.18 [0.89, 1.58] 1.82 [1.33, 2.48] 3.17 [1.18, 8.55] 1.21 [0.97, 1.52] 1.04 [0.87, 1.26] 2.50 [1.09, 57, 1.60] 1.18 [0.94, 1.48] 1.69 [1.30, 2.19] 1.09 [0.79, 1.52] 2.41 [1.67, 3.49] 1.60 [1.05, 2.43] 1.60 [1.18, 2.24] 1.31 [0.96, 1.78] 1.10 [0.70, 1.73] 1.16 [0.90, 1.49] 1.43 [1.14, 1.78] 1.09 [0.72, 1.65] 1.29 [0.86, 1.94] 1.12 [0.67, 1.89] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.07, 1.78] 1.38 [1.09, 1.78] 1.39 [1.09, 1.79] 1.31 [1.09, 1.79] 1.32 [1.09, 1.79] 1.33 [1.09, 1.78] 1.34 [1.12, 1.94] 1.45 [1.12, 1.94] 1.46 [0.71, 3.78] 1.60 [1.03, 2.51] 1.43 [0.93, 2.19] 0.87 [0.41, 1.84] 3.55 [1.45, 8.68]   |   |
| innemann 2008 ose 2008 urke 2002 yerley 1988 L3-20098-022 L3-20098-024 laghorn 1992b layton 2006_study 1 layton 2006_study 2 etke 2004 ube 2010 unbar 1993 li Lilly HMAT-A msley 2018 abre 1995a ava 1998a orest Laboratories 2000 orest Research Institute 2005 oldstein 2004 ual 2003 liiguchi 2009 lirayasu 2011a lirayasu 2011b efferson 2000 asper 2012 atz 2004 ramer 1998 ramzer 1998 arazler 2006_Group A am 2016 acias-Cortes 2015 lendels 1999 undt 2012 Y-1045/BRL-029060/CPMS-251 IY-1045/BRL-029060/I (PAR 128) lemeroff 2007 KD20006 (NCT00048204) yth 1992 lie 1997 KR 01 001 (GSK & FDA) erahia 2006 esselow 1989a esselow 1989a esselow 19898 espaport 2009 atti 2011_study 096 awindran 1995 eimherr 1990 eimherr 1990 atti 2011_study 096 awindran 1995 eimherr 1990 atti 2011_study 096 awindran 1995 eimherr 1990   | 99<br>99<br>99<br>99<br>99<br>99<br>99<br>99<br>99<br>99<br>99<br>99<br>99   | 132<br>379<br>32<br>137<br>148<br>36<br>62<br>170<br>89<br>278<br>109<br>257<br>44<br>148<br>205<br>331<br>140<br>28<br>89<br>31<br>46<br>289  | 51 33 34 4 69 91 69 64 41 59 64 41 59 66 66 66 45 66 66 66 66 66 67 67 67 67 67 67 67 67  | 39 135 127 29 149 158 36 36 141 137 79 31 138 171 90 135 70 89 39 36 146 105 71 25 70 100 30 30 43 290   | 1.0% 1.8% 1.6% 0.2% 2.3% 2.5% 2.3% 2.5% 1.5% 1.3% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1   | 1.33 [0.86, 2.07] 1.18 [0.89, 1.58] 1.82 [1.33, 2.48] 3.17 [1.18, 8.55] 1.21 [0.97, 1.52] 1.04 [0.87, 1.26] 2.50 [1.09, 57, 1.60] 1.18 [0.94, 1.48] 1.69 [1.30, 2.19] 1.09 [0.79, 1.52] 2.41 [1.67, 3.49] 1.60 [1.05, 2.43] 1.60 [1.18, 2.24] 1.31 [0.96, 1.78] 1.10 [0.70, 1.73] 1.16 [0.90, 1.49] 1.43 [1.14, 1.78] 1.09 [0.72, 1.65] 1.29 [0.86, 1.94] 1.12 [0.67, 1.89] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.06, 1.78] 1.37 [1.07, 1.78] 1.38 [1.09, 1.78] 1.39 [1.09, 1.79] 1.31 [1.09, 1.79] 1.32 [1.09, 1.79] 1.33 [1.09, 1.78] 1.34 [1.12, 1.94] 1.45 [1.12, 1.94] 1.46 [0.71, 3.78] 1.60 [1.03, 2.51] 1.43 [0.93, 2.19] 0.87 [0.41, 1.84] 3.55 [1.45, 8.68]   |   |
| ose 2008 urke 2002 urke 2002 11 yerley 1988 L3-20098-022 L3-20098-024 laghorn 1992b layton 2006_study 1 layton 2006_study 2 etke 2004 urbe 2010 unbar 1993 II Lilly HMAT-A msley 2018 abre 1995a ava 1998a orest Laboratories 2000 orest Research Institute 2005 oldstein 2004 uala 2003 liguchi 2009 lirayasu 2011a lirayasu 2011b lirayasu 2011b lirayasu 2011b lirayasu 2011b lirayasu 2011b lirayasu 2011b lirayasu 2011c lirayasu 2015 ata 2004 ta 2004 ta 2004 ta 2005 ta 2006_Group A am 2016 lacias-Cortes 2015 lathews 2015 lendels 1999 lundt 2012 Y-1042/BRL-029060/CPMS-251 Y-1045/BRL-029060/CPMS-251 Y-1045/BRL-029060/I (PAR 128) emeroff 2007 lice 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 1989a eselow 1989b lapaport 2009 atti 2011_study 096 avindran 1995 eimherr 1990   | 99<br>99<br>99<br>99<br>99<br>99<br>99<br>99<br>99<br>99<br>99<br>99<br>99   | 379 32 137 148 36 142 86 62 170 278 89 99 278 274 33 87 44 148 205 361 310 140 28 89 31 46 289   | 33 4<br>4 99 91 6 699 644 411 599 30 32 24 32 77 155 66 66 33 32 77 155 66 66 62 02 26 10 0 12 14 2   | 127<br>29<br>149<br>158<br>36<br>141<br>137<br>93<br>138<br>171<br>91<br>129<br>135<br>70<br>39<br>39<br>146<br>105<br>71<br>25<br>70<br>100<br>30<br>30<br>43<br>29<br>20   | 1.6% 0.2% 2.3% 2.8% 0.3% 2.5% 2.3% 2.0% 1.5% 1.1% 1.6% 0.9% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1  | 1.82 [1.33, 2.48] 3.17 [1.18, 8.55] 1.21 [0.97, 1.52] 1.04 [0.87, 1.26] 2.50 [1.09, 5.71] 1.30 [1.05, 1.60] 1.18 [0.94, 1.48] 1.69 [1.30, 2.19] 1.09 [0.79, 1.52] 2.41 [1.67, 3.49] 1.60 [1.05, 2.49] 1.61 [1.67, 3.49] 1.62 [1.18, 2.24] 1.31 [0.96, 1.78] 1.10 [0.70, 1.73] 1.16 [0.90, 1.49] 1.43 [1.14, 1.78] 1.09 [0.72, 1.65] 1.29 [0.86, 1.94] 1.12 [0.67, 1.89] 1.37 [1.06, 1.78] 1.03 [0.86, 1.23] 1.37 [1.06, 1.78] 1.03 [0.86, 1.23] 1.37 [1.06, 1.78] 1.04 [1.71, 3.78] 1.60 [1.02, 1.82] 1.48 [1.12, 1.94] 1.64 [0.71, 3.78] 1.60 [1.03, 2.51] 1.43 [0.93, 2.19] 0.87 [0.41, 1.84] 3.55 [1.45, 8.68]   |   |
| urke 2002 yerley 1988 L3-20098-022 L3-20098-024 laghorn 1992b laghorn 1992b layton 2006_study 1 layton 2006_study 2 etke 2004 ube 2010 unbar 1993 li Lilly HMAT-A msley 2018 abre 1995a ava 1998a orest Laboratories 2000 orest Research Institute 2005 oldstein 2004 ual 2003 iguchi 2009 iirayasu 2011a iirayasu 2011b iirayasu 2011b iirayasu 2011b iirayasu 2011b iirayasu 2016 lacias-Cortes 2015 athews 2015 athews 2015 lendels 1999 undt 2012 'Y-1042/BRL-029060/CPMS-251 YY-1045/BRL-029060/I (PAR 128) emeroff 2007 ikD20006 (NCT00048204) yth 1992 lite 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 1989a eselow 1989a eselow 1989b lapaport 2009 atti 2011_study 096 eimherr 1990  | 99 44<br>77 79 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9   | 379 32 137 148 36 142 86 62 170 278 89 99 278 274 33 87 44 148 205 361 310 140 28 89 31 46 289   | 33 4<br>4 99 91 6 699 644 411 599 30 32 24 32 77 155 66 66 33 32 77 155 66 66 62 02 26 10 0 12 14 2   | 127<br>29<br>149<br>158<br>36<br>141<br>137<br>93<br>138<br>171<br>91<br>129<br>135<br>70<br>39<br>39<br>146<br>105<br>71<br>25<br>70<br>100<br>30<br>30<br>43<br>29<br>20   | 1.6% 0.2% 2.3% 2.8% 0.3% 2.5% 2.3% 2.0% 1.5% 1.1% 1.6% 0.9% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2.1  | 1.82 [1.33, 2.48] 3.17 [1.18, 8.55] 1.21 [0.97, 1.52] 1.04 [0.87, 1.26] 2.50 [1.09, 5.71] 1.30 [1.05, 1.60] 1.18 [0.94, 1.48] 1.69 [1.30, 2.19] 1.09 [0.79, 1.52] 2.41 [1.67, 3.49] 1.60 [1.05, 2.49] 1.61 [1.67, 3.49] 1.62 [1.18, 2.24] 1.31 [0.96, 1.78] 1.10 [0.70, 1.73] 1.16 [0.90, 1.49] 1.43 [1.14, 1.78] 1.09 [0.72, 1.65] 1.29 [0.86, 1.94] 1.12 [0.67, 1.89] 1.37 [1.06, 1.78] 1.03 [0.86, 1.23] 1.37 [1.06, 1.78] 1.03 [0.86, 1.23] 1.37 [1.06, 1.78] 1.04 [1.71, 3.78] 1.60 [1.02, 1.82] 1.48 [1.12, 1.94] 1.64 [0.71, 3.78] 1.60 [1.03, 2.51] 1.43 [0.93, 2.19] 0.87 [0.41, 1.84] 3.55 [1.45, 8.68]   |   |
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| L3-20098-022 L3-20098-024 L3-20098-029 L3-20 | 7  | 137<br>148<br>36<br>142<br>149<br>86<br>62<br>170<br>89<br>99<br>257<br>274<br>33<br>87<br>44<br>148<br>205<br>361<br>310<br>140<br>28<br>72<br>89<br>31<br>46<br>289  | 69 91 66 69 64 41 56 66 66 66 66 66 66 66 66 66 66 66 66  | 149<br>158<br>341<br>137<br>93<br>138<br>171<br>90<br>107<br>91<br>129<br>135<br>70<br>89<br>39<br>146<br>105<br>71<br>124<br>105<br>71<br>100<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>3  | 2.3% 2.8% 0.3% 2.5% 2.3% 2.0% 1.5% 1.3% 1.1% 2.1% 2.1% 2.1% 2.1% 2.1% 2.9% 1.18% 1.9% 0.3% 1.9% 0.3% 3.3%   | 1.21 (0.97, 1.52) 1.04 (0.87, 1.26) 2.50 (1.09, 5.71) 1.30 (1.05, 1.60) 1.18 (0.94, 1.48) 1.69 (1.30, 2.19) 1.09 (0.79, 1.52) 2.41 (1.67, 3.49) 1.60 (1.05, 2.43) 1.62 (1.18, 2.24) 1.31 (0.96, 1.78) 1.10 (0.70, 1.73) 1.16 (0.90, 1.49) 1.43 (1.14, 1.78) 1.09 (0.72, 1.65) 1.29 (0.86, 1.94) 1.12 (0.67, 1.89) 1.37 (1.06, 1.78) 1.37 (1.06, 1.78) 1.37 (1.06, 1.78) 1.37 (1.06, 1.78) 1.37 (1.06, 1.78) 1.37 (1.06, 1.78) 1.37 (1.07, 1.78) 1.38 (1.02, 1.82) 1.49 (1.71, 3.78) 1.60 (1.03, 2.51) 1.43 (0.93, 2.19) 0.87 (0.41, 1.84) 3.55 (1.45, 8.68)   |   |
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| abre 1995a ava 1998a crost Laboratories 2000 drest Research Institute 2005 ordest Research Institute 2005 ordestein 2002 ordestein 2004 ual 2003 iiguchi 2009 iirayasu 2011a iirayasu 2011b efferson 2000 asper 2012 atz 2004 tamer 1998 ranzler 2006_Group A arm 2016 acias-Cortes 2015 lathews 2015 lathews 2015 lathews 2015 lathews 2015 lathews 2015 lathered 2007 iversity 2006_Group A arm 2016 acias-Cortes 2015 lathews 2015 lathews 2015 lathews 2015 lathews 2016 lathered 2007 iversity 2006_Group A arm 2016 acias-Cortes 2015 lathews 2015 lathews 2015 lathews 2016 lathews 2016 lathered 2007 iversity 2006 lemented 2007 iversity 2007  | 8 : : : : : : : : : : : : : : : : : : :  | 278<br>109<br>257<br>274<br>33<br>87<br>44<br>148<br>205<br>361<br>310<br>140<br>28<br>72<br>89<br>31<br>46<br>289   | 32<br>10<br>51<br>56<br>33<br>27<br>15<br>56<br>66<br>45<br>36<br>20<br>20<br>20<br>5   | 91<br>19<br>129<br>135<br>70<br>89<br>39<br>146<br>105<br>124<br>105<br>71<br>25<br>70<br>100<br>30<br>43<br>290   | 1.7%<br>0.9%<br>2.1%<br>1.1%<br>1.1%<br>2.1%<br>2.1%<br>2.1%<br>1.8%<br>1.9%<br>1.0%<br>1.0%<br>0.3%<br>3.3%  | 1.31 [0.96, 1.78]<br>1.10 [0.70, 1.73]<br>1.16 [0.90, 1.49]<br>1.43 [1.14, 1.78]<br>1.09 [0.72, 1.65]<br>1.29 [0.86, 1.94]<br>1.12 [0.67, 1.89]<br>1.37 [1.06, 1.76]<br>1.36 [1.02, 1.82]<br>1.37 [1.06, 1.76]<br>1.36 [1.02, 1.82]<br>1.48 [1.12, 1.94]<br>1.64 [0.71, 3.78]<br>1.60 [1.03, 2.51]<br>1.43 [0.93, 2.19]<br>0.87 [0.41, 1.84]<br>3.55 [1.45, 8.68]   |   |
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| Irayasu 2011b 17  efferson 2000 14  asper 2012 15  atz 2004  ramer 1998 16  lacias-Cortes 2015  lathews 2015 16  lacias-Cortes 2015  lathews 2015 17  lathews 2 | 9 :<br>5 :<br>6 :<br>1<br>3<br>3<br>3<br>9<br>9  | 361<br>310<br>140<br>28<br>72<br>89<br>31<br>46<br>289   | 45<br>36<br>33<br>6<br>20<br>26<br>10<br>5  | 124<br>105<br>71<br>25<br>70<br>100<br>30<br>43<br>290   | 2.1%<br>1.8%<br>1.9%<br>0.3%<br>1.0%<br>0.4%<br>0.3%<br>3.3%  | 1.37 [1.06, 1.76]<br>1.36 [1.02, 1.82]<br>1.48 [1.12, 1.94]<br>1.64 [0.71, 3.78]<br>1.60 [1.03, 2.51]<br>1.43 [0.93, 2.19]<br>0.87 [0.41, 1.84]<br>3.55 [1.45, 8.68]  |   |
| efferson 2000 14 asper 2012 3 asper 2014 5 asper 2015 4 tamer 1998 5 tanzler 2006_Group A am 2016 lacias-Cortes 2015 lathews 2015 15 lathews 2015 17 lathews 2015 17 lathews 2015 17 lathews 2016 17 lathews 2017 18 lathews 2016 17 lathews 2017 18 lathews 2016 18 lathews 2 | 5 :<br>6 :<br>1 :<br>3 :<br>3 :<br>9 :<br>9 :  | 310<br>140<br>28<br>72<br>89<br>31<br>46<br>289  | 36<br>33<br>6<br>20<br>26<br>10<br>5  | 105<br>71<br>25<br>70<br>100<br>30<br>43<br>290  | 1.8%<br>1.9%<br>0.3%<br>1.0%<br>1.0%<br>0.4%<br>0.3%<br>3.3%  | 1.36 [1.02, 1.82]<br>1.48 [1.12, 1.94]<br>1.64 [0.71, 3.78]<br>1.60 [1.03, 2.51]<br>1.43 [0.93, 2.19]<br>0.87 [0.41, 1.84]<br>3.55 [1.45, 8.68]   | <del>  -</del><br> -<br> <br>   |
| asper 2012 atz 2004 atz 2004 atz 2004 atz 2006_Group A am 2016 lacias-Cortes 2015 athews 2015 lendels 1999 undt 2012 Y-1042/BRL-029060/CPMS-251 Y-1045/BRL-029060/1 (PAR 128) lemenoff 2007 lkD20006 (NCT00048204) yth 1992 lilie 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 1989b lapaport 2009 atti 2011_study 096 avindran 1995 elemenof 998 eselow 1995 elemenof 2009 atti 2011_study 096 avindran 1995 elemenof 998 eselow 1995 elemenof 2009 atti 2011_study 096 avindran 1995 elemenof 998 eselow 1995 elemenof 998 elemenof 2009 atti 2011_study 096 elemenof 998 elemeno | 6<br>1<br>3<br>3<br>9<br>9   | 140<br>28<br>72<br>89<br>31<br>46<br>289   | 33<br>6<br>20<br>26<br>10<br>5  | 71<br>25<br>70<br>100<br>30<br>43<br>290   | 1.9%<br>0.3%<br>1.0%<br>1.0%<br>0.4%<br>0.3%<br>3.3%  | 1.48 [1.12, 1.94]<br>1.64 [0.71, 3.78]<br>1.60 [1.03, 2.51]<br>1.43 [0.93, 2.19]<br>0.87 [0.41, 1.84]<br>3.55 [1.45, 8.68]  |   |
| atz 2004 ramer 1998 ranzler 2006_Group A am 2016 acias-Cortes 2015 lathews 2015 endels 1999 undt 2012 Y-1045/BRL-029060/CPMS-251 Y-1045/BRL-029060/I (PAR 128) emeroff 2007 kD20006 (NCT00048204) yth 1992 lile 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 1989a eselow 1989b lapaport 2009 atti 2011_study 096 awindran 1996 eimherr 1990   | 1<br>3<br>3<br>9<br>9  | 28<br>72<br>89<br>31<br>46<br>289  | 6<br>20<br>26<br>10<br>5<br>142   | 25<br>70<br>100<br>30<br>43<br>290   | 0.3%<br>1.0%<br>1.0%<br>0.4%<br>0.3%<br>3.3%  | 1.64 [0.71, 3.78]<br>1.60 [1.03, 2.51]<br>1.43 [0.93, 2.19]<br>0.87 [0.41, 1.84]<br>3.55 [1.45, 8.68]   |   |
| ramer 1998 ramzer 2006_Group A am 2016 acias-Cortes 2015 athews 2015 endels 1999 undt 2012 Y-1042/BRL-029060/CPMS-251 Y-1045/BRL-029060/1 (PAR 128) emeroff 2007 ibrenberg 2007 ikD 20006 (NCT00048204) Yth 1992 lille 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 1989b apaport 2009 atti 2011_study 096 awindran 1995 elemherr 1990   | 3<br>3<br>9<br>9   | 72<br>89<br>31<br>46<br>289  | 20<br>26<br>10<br>5<br>142  | 70<br>100<br>30<br>43<br>290   | 1.0%<br>1.0%<br>0.4%<br>0.3%<br>3.3%  | 1.60 [1.03, 2.51]<br>1.43 [0.93, 2.19]<br>0.87 [0.41, 1.84]<br>3.55 [1.45, 8.68]  |   |
| ranzler 2006_Group A am 2016 acias-Cortes 2015 lathews 2015 lendels 1999 lundt 2012 Y-1042/BRL-029060/CPMS-251 Y-1045/BRL-029060/1 (PAR 128) lemenoff 2007 likD20006 (NCT00048204) yth 1992 lilie 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 1989b lapaport 2009 atti 2011_study 096 awindran 1995 eimherr 1990  | 3<br>9<br>9  | 89<br>31<br>46<br>289  | 26<br>10<br>5<br>142  | 100<br>30<br>43<br>290   | 1.0%<br>0.4%<br>0.3%<br>3.3%  | 1.43 [0.93, 2.19]<br>0.87 [0.41, 1.84]<br>3.55 [1.45, 8.68]   | +   |
| am 2016 acias-Cortes 2015 acias-Cortes 2015 lendels 1999 undt 2012 Y-1045/BRL-029060/CPMS-251 Y-1045/BRL-029060/1 (PAR 128) lemeroff 2007 kD20006 (NCT00048204) yth 1992 lile 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 1989b lapaport 2009 atti 2011_study 096 avindran 1995 elemerof 1990   | 9<br>9<br>6 :  | 31<br>46<br>289  | 10<br>5<br>142  | 30<br>43<br>290  | 0.4%<br>0.3%<br>3.3%  | 0.87 [0.41, 1.84]<br>3.55 [1.45, 8.68]  | <u> </u>  |
| lacias-Cortes 2015 athews 2015 athews 2015 athews 2015 athews 2015 athews 2015 lendels 1999 undt 2012 Y-1042/IBRL-029060/CPMS-251 Y-1045/IBRL-029060/1 (PAR 128) emeroff 2007 lierenberg 2007 KD20006 (NCT00048204) yith 1992 lie 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 1989b apaport 2009 atti 2011_study 096 avindran 1995 leimherr 1990  | 9<br>6 :   | 46<br>289  | 5<br>142  | 43<br>290  | 0.3%<br>3.3%  | 3.55 [1.45, 8.68]   | i ——  |
| lathews 2015 11 endels 1999 12 undt 2012 12 Y-1042/BRL-029060/CPMS-251 13 Y-1045/BRL-029060/1 (PAR 128) 146 lemeroff 2007 15 IED 1997 16 AR 01 001 (GSK & FDA) 18 erahia 2006 1999 16 eselow 1989a 1999 16 awindran 1995 16 eimherr 1990 16 eimherr 1990 17  | 6 :  | 289  | 142   | 290  | 3.3%  |   |   |
| lendels 1999 undt 2012 Y-1045/BRL-029060/CPMS-251 IY-1045/BRL-029060/1 (PAR 128) 46 Iemeroff 2007 IkD20006 (NCT00048204) Iyth 1992 Illie 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 19898 Iapaport 2009 atti 2011_study 096 evinder 1995 evinder 1996  |  |  |   |  |   | 1.24 [1.07.1.44]  |   |
| undt 2012  | 7  | 0.0  | 24  | 91   | 4.400   | 1.24 [1.07, 1.44]   | l <b>–</b>  |
| undt 2012  |  | 89   |   |  | 1.1%  | 1.58 [1.03, 2.41]   |   |
| Y-1042/BRL-029060/CPMS-251   | 3  | 80   | 20  | 85   | 0.9%  | 1.75 [1.10, 2.79]   |   |
| Y-1045/BRL-029060/1 (PAR 128)  |  | 125  | 44  | 129  | 1.7%  | 1.31 [0.96, 1.79]   |   |
| lemeroff 2007 lierenberg 2007 lierenberg 2007 lkth 20006 (NCT00048204) lyth 1992 llie 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 1989b lapaport 2009 10 latti 2011_study 096 lawindran 1995 leimherr 1990  |  | 708  | 69  | 140  | 2.9%  | 1.32 [1.11, 1.58]   |   |
| Ierenberg 2007   |  | 104  | 37  | 102  | 1.5%  | 1.19 [0.85, 1.67]   |   |
| KD20006 (NCT00048204)  |  | 274  | 36  | 137  |   |   |   |
| yth 1992 lie 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 1989b apaport 2009 10 atti 2011_study 096 avindran 1995 leimherr 1990  |  |  |   |  | 1.6%  | 1.31 [0.94, 1.81]   |   |
| lie 1997 AR 01 001 (GSK & FDA) erahia 2006 eselow 1989a eselow 1989b apaport 2009 10 apatiti 2011_study 096 avindran 1995 eimherr 1990   |  | 125  | 59  | 125  | 2.0%  | 0.97 [0.74, 1.26]   |   |
| AR 01 001 (GSK & FDA) erahia 2006  |  | 98   | 9   | 51   | 0.5%  | 1.85 [0.96, 3.57]   |   |
| erahia 2006 6 eselow 1989a eselow 1989b (apaport 2009 10 atti 2011_study 096 awindran 1995 eimherr 1990  |  | 129  | 45  | 129  | 1.8%  | 1.58 [1.19, 2.09]   | · I   |
| eselow 1989a eselow 1989b apaport 2009 10 atti 2011_study 096 avindran 1995 eimherr 1990   | 1  | 25   | 8   | 25   | 0.4%  | 1.38 [0.67, 2.83]   |   |
| eselow 1989b ( apaport 2009 10 atti 2011_study 096 ( avindran 1995 ( eimherr 1990 (  | 9  | 97   | 51  | 99   | 2.1%  | 1.18 [0.92, 1.51]   |   |
| apaport 2009 10<br>atti 2011_study 096 6<br>avindran 1995 5<br>eimherr 1990 5  | 7  | 34   | 14  | 39   | 0.7%  | 1.39 [0.81, 2.38]   | l <del> </del>  |
| atti 2011_study 096<br>avindran 1995<br>eimherr 1990   | 9  | 40   | 14  | 42   | 0.7%  | 1.43 [0.83, 2.44]   | l <del> </del>  |
| avindran 1995<br>leimherr 1990   | 0 '  | 177  | 71  | 180  | 2.4%  | 1.43 [1.15, 1.79]   |   |
| avindran 1995<br>leimherr 1990   | 5  | 113  | 73  | 123  | 2.5%  | 0.97 [0.78, 1.20]   |   |
| eimherr 1990   | 7  | 40   | 7   | 26   | 0.4%  | 1.58 [0.76, 3.27]   |   |
|  |  | 149  | 49  | 150  | 1.9%  | 1.58 [1.20, 2.09]   |   |
|  | 2  | 55   | 10  | 56   | 0.5%  | 2.24 [1.17, 4.28]   |   |
|  |  | 103  | 41  | 98   | 1.7%  | 1.21 [0.89, 1.63]   |   |
|  | 7  | 99   | 23  | 95   | 0.9%  | 1.13 [0.70, 1.82]   |   |
|  | 5  | 39   | 8   | 38   | 0.4%  | 1.83 [0.88, 3.80]   |   |
|  |  | 185  |   |  |   | 1.80 [1.30, 2.49]   |   |
|  |  |  | 39  | 169  | 1.6%  |   |   |
|  | 5  | 37   | 28  | 75   | 0.8%  | 1.09 [0.67, 1.77]   |   |
| ollefson 1993/1995 12  |  | 336  | 90  | 335  | 2.3%  | 1.34 [1.07, 1.68]   |   |
|  | 8  | 39   | 12  | 38   | 0.8%  | 2.27 [1.37, 3.78]   |   |
| -  |  | 157  | 78  | 157  | 2.6%  | 1.17 [0.95, 1.43]   |   |
|  |  | 155  | 78  | 154  | 2.5%  | 1.12 [0.91, 1.38]   |   |
| /ernicke 1987 11   |  | 308  | 9   | 48   | 0.6%  | 1.94 [1.06, 3.56]   |   |
|  |  | 189  | 18  | 78   | 1.0%  | 2.04 [1.32, 3.14]   |   |
| ubtotal (95% CI)   | 8  | 8741   |   | 6373   | 92.3%   | 1.35 [1.28, 1.42]   |   |
| otal events 440  |  | 45   | 2370  |  |   |   |   |
| leterogeneity: Tau² = 0.02; Chi² = 102.18, df = 61 (P = 0.000<br>est for overall effect: Z = 10.95 (P < 0.00001)   |  | = 40%  |   |  |   |   |   |
| otal (05% CI)  | 3); I² =   | 0.402  |   | 6075   | 100.0%  | 4 33 [4 37 4 40]  |   |
| otal (95% CI)  |  |  |   | 00/5   | 100.0%  | 1.33 [1.27, 1.40]   | <b>                                   </b>                                      |
| otal events 475  | 9.   | 9403   | 2584  |  |   |   |   |
| leterogeneity: Tau² = 0.01; Chi² = 104.09, df = 65 (P = 0.001<br>est for overall effect: Z = 11.37 (P < 0.00001)   | 9.<br>6  |  |   |  |   |   |   |

# Primary care versus secondary care subgroup analysis for Comparison 1c. SSRIs versus Tricyclic Antidepressants (TCAs)

Figure 55: Depression symptomatology at endpoint

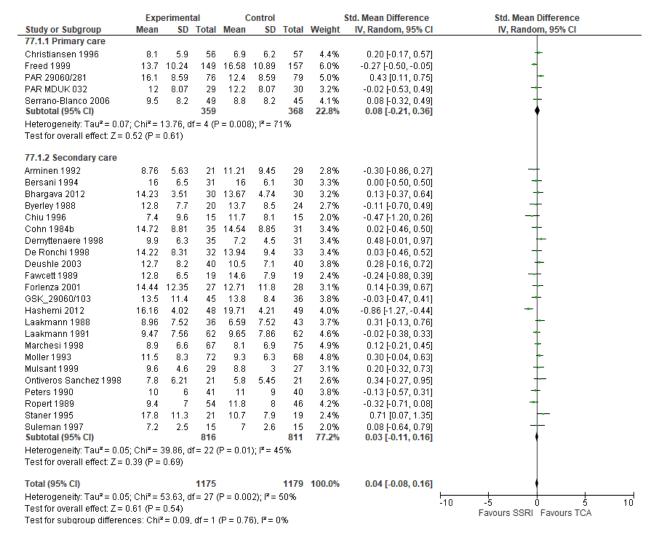


Figure 56: Depression symptomatology change score

|  |              | xperimental     |                  |                    | Control    |                   |                      | Std. Mean Difference                              |     |           | Difference         |  |
|--|--------------|-----------------|------------------|--------------------|------------|-------------------|----------------------|---|-----|-----------|--------------------|--|
| Study or Subgroup  | Mean         | SD              | Total            | Mean               | \$D        | Total             | Weight               | IV, Random, 95% CI                                |     | IV, Rande | m, 95% CI          |  |
| 77.2.1 Primary care  |              |                 |                  |                    |            |                   |                      |   |     |           |                    |  |
| reed 1999  |              | 6.81452126      |                  |                    | 7.61073912 | 157               | 4.7%                 | -0.36 [-0.59, -0.14]                              |     | •         | 1                  |  |
| Serrano-Blanco 2006<br>Subtotal (95% CI)                       | -12.7        | 6.17413962      | 49<br><b>198</b> | -12.9              | 6.22253967 | 45<br><b>202</b>  | 3.4%<br><b>8.1%</b>  | 0.03 [-0.37, 0.44]<br>- <b>0.20 [-0.58, 0.18]</b> |     |           |                    |  |
| Heterogeneity: Tau <sup>2</sup> = 0.05;                        | $Chi^2 = 2.$ | 77, df = 1 (P = | 0.10); [         | <sup>2</sup> = 64% |            |                   |                      |   |     |           |                    |  |
| est for overall effect: Z = 1.                                 |              |                 | ,,               |                    |            |                   |                      |   |     |           |                    |  |
| 7.2.2 Secondary care   |              |                 |                  |                    |            |                   |                      |   |     |           |                    |  |
| 29060/299  | -14.3        | 9.35            | 102              | -14.39             | 8.39       | 100               | 4.3%                 | 0.01 [-0.27, 0.29]                                |     |           | †                  |  |
| 29060 07 001   | -13.08       | 10.2191         | 12               | -13.31             | 11.1051    | 13                | 1.7%                 | 0.02 [-0.76, 0.81]                                |     | -         | +                  |  |
| Akhondzadeh 2003   | -16.82       | 11.08           | 17               | -20.3              | 8.12       | 20                | 2.1%                 | 0.36 [-0.30, 1.01]                                |     |           | <del> </del>       |  |
| Beasley 1993b  | -12.9        | 9.9             | 65               | -11.6              | 10.3       | 71                | 3.9%                 | -0.13 [-0.46, 0.21]                               |     | -         | +                  |  |
| Bersani 1994   | -17          | 4.33128157      | 31               | -16                | 4.04103947 | 30                | 2.8%                 | -0.24 [-0.74, 0.27]                               |     | -         | †                  |  |
| 3hargava 2012  | -11.7        | 2.7227835       | 30               | -13.33             | 3.26046009 | 30                | 2.8%                 | 0.54 [0.02, 1.05]                                 |     |           | <del> </del>       |  |
| Chiu 1996  | -20.2        | 9.1             | 15               | -15.3              | 8.4        | 15                | 1.8%                 | -0.54 [-1.28, 0.19]                               |     | _         | +                  |  |
| Cohn 1990b   | -13.3        | 7.76            | 121              | -14.2              | 7.76       | 64                | 4.1%                 | 0.12 [-0.19, 0.42]                                |     |           | +                  |  |
| Demyttenaere 1998  |              | 4.21366824      | 35               |                    | 2.99416098 | 31                | 2.9%                 | 0.45 [-0.04, 0.94]                                |     |           | <del> </del>       |  |
| De Ronchi 1998   |              | 5.50659605      |                  | -12.56             | 6.3688225  | 33                | 2.9%                 | 0.20 [-0.29, 0.68]                                |     |           | <del> </del> -     |  |
| eushle 2003  |              | 5.99332963      | 40               | -13.5              | 4.7042534  | 40                | 3.2%                 | 0.48 [0.03, 0.92]                                 |     |           | -                  |  |
| abre 1992  | -9.13        | 8.14            | 38               | -7.62              | 8.09       | 37                | 3.1%                 | -0.18 [-0.64, 0.27]                               |     | _         | +                  |  |
| awcett 1989  |              | 4.69041576      | 19               |                    | 5.94011784 | 19                | 2.2%                 | -0.35 [-0.99, 0.29]                               |     | _         | 1                  |  |
| orlenza 2001   | -15.85       | 11.89           |                  | -15.03             | 10.46      | 28                | 2.7%                 | -0.07 [-0.60, 0.46]                               |     | -         | <b>↓</b>           |  |
| SK_29060/103   | -17.8        | 10.73           | 45               | -17.1              | 9.6        | 36                | 3.2%                 | -0.07 [-0.51, 0.37]                               |     |           | ↓                  |  |
| Hashemi 2012   | -16.96       | 4.96            |                  | -13.14             | 4.68       | 49                | 3.4%                 | -0.79 [-1.20, -0.37]                              |     | -         |                    |  |
| Marchesi 1998  |              | 4.37264222      | 67               |                    | 4.59401785 | 75                | 4.0%                 | 0.13 [-0.20, 0.46]                                |     |           | Ļ                  |  |
| MDF/29060/III/070/88/MC  | -10.0        | 8.59            | 24               | -15                | 8.22       | 20                | 2.3%                 |   |     | _         | ]                  |  |
|  |              |                 |                  | -10.6              |            |                   |                      | -0.58 [-1.19, 0.02]                               |     |           | Ţ                  |  |
| Miura 2000   | -9.2         | 11.5            | 102              |                    | 11.1       | 114               | 4.4%                 | 0.12 [-0.14, 0.39]                                |     |           |                    |  |
| Moller 1993  |              | 5.49272246      | 72               |                    | 4.49110232 | 68                | 3.9%                 | 0.34 [0.00, 0.67]                                 |     |           |                    |  |
| 10ller 1998  | -13.6        | 9.3             | 62               | -16.5              | 9.4        | 59                | 3.8%                 | 0.31 [-0.05, 0.67]                                |     |           |                    |  |
| Mulsant 1999   | -11.3        | 3.0528675       | 29               |                    | 2.58069758 | 27                | 2.6%                 | 0.80 [0.25, 1.35]                                 |     |           |                    |  |
| Preskorn 1991  | -10.1        | 7.8             | 29               | -7.9               | 6.1        | 31                | 2.8%                 | -0.31 [-0.82, 0.20]                               |     | _         | T                  |  |
| Reimherr 1990  | -11.66       | 8.24            |                  | -12.64             | 7.97       | 144               | 4.6%                 | 0.12 [-0.11, 0.35]                                |     |           | Ť                  |  |
| Ropert 1989  |              | 4.77074418      | 54               |                    | 5.38516481 | 46                | 3.5%                 | -0.31 [-0.71, 0.08]                               |     | -         | †                  |  |
| SER 315 (FDA)  | -8.9         | 4.52            | 76               | -11.6              | 11.49      | 70                | 4.0%                 | 0.31 [-0.01, 0.64]                                |     |           | <u></u>            |  |
| Staner 1995  |              | 7.93851372      | 21               |                    | 5.56866232 | 19                | 2.2%                 | 0.72 [0.08, 1.37]                                 |     |           | _                  |  |
| Stark 1985   | -11          | 10.1            | 185              | -12                | 10.1       | 185               | 4.8%                 | 0.10 [-0.11, 0.30]                                |     |           | †                  |  |
| Buleman 1997<br>Bubtotal (95% CI)                              | -18.2        | 1.68522996      | 15<br>1555       | -15.9              | 2.31516738 | 15<br><b>1489</b> | 1.7%<br><b>91.9%</b> | -1.11 [-1.88, -0.33]<br>0.04 [-0.08, 0.17]        |     |           |                    |  |
| Heterogeneity: Tau² = 0.06;<br>Fest for overall effect: Z = 0. |              |                 | o.00             | i001); l²÷         | = 61%      |                   |                      |   |     |           |                    |  |
| Γotal (95% CI)   |              |                 | 1753             |                    |            | 1691              | 100.0%               | 0.02 [-0.10, 0.14]                                |     |           |                    |  |
| Heterogeneity: Tau² = 0.07;<br>Test for overall effect: Z = 0. |              |                 | o.00             | 1001); l²:         | = 65%      |                   |                      |   | -10 | -5        | 0 5<br>Favours TCA |  |

Figure 57: Remission

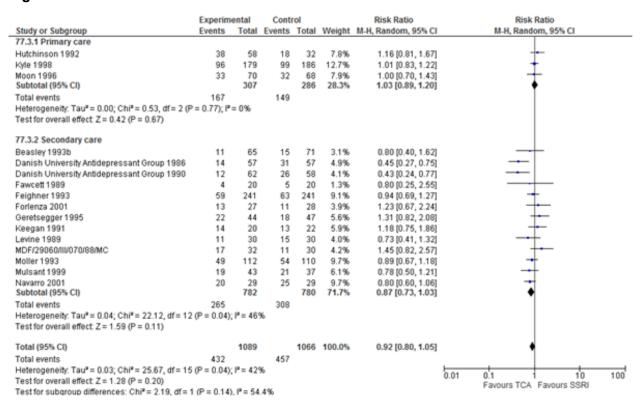


Figure 58: Response

|   | Experim      | ental      | Contr      | ol                  |               | Risk Ratio                             |      | Risk Ratio                              |     |
|---|--------------|------------|------------|---------------------|---------------|--|------|---|-----|
| Study or Subgroup                       | Events       | Total      | Events     | Total               | Weight        | M-H, Random, 95% CI                    |      | M-H, Random, 95% CI                     |     |
| 77.4.1 Primary care                     |              |            |            |                     |               |  |      |   |     |
| Christiansen 1996                       | 46           | 71         | 48         | 73                  | 7.0%          | 0.99 [0.78, 1.25]                      |      | +                                       |     |
| Hutchinson 1992                         | 35           | 58         | 18         | 32                  | 2.9%          | 1.07 [0.74, 1.55]                      |      | +                                       |     |
| Moon 1994                               | 27           | 51         | 27         | 55                  | 2.9%          | 1.08 [0.74, 1.57]                      |      | +                                       |     |
| Moon 1996                               | 32           | 70         | 30         | 68                  | 2.9%          | 1.04 [0.72, 1.50]                      |      | +                                       |     |
| Rosenberg 1994                          | 201          | 380        | 45         | 92                  | 7.6%          | 1.08 [0.86, 1.36]                      |      | +                                       |     |
| Subtotal (95% CI)                       | 201          | 630        |            | 320                 | 23.2%         | 1.04 [0.92, 1.19]                      |      | <b>+</b>                                |     |
| Total events                            | 341          |            | 168        |                     |               |  |      |   |     |
| Heterogeneity: Tau <sup>2</sup> = 0.00; | Chi2 = 0.3   | 7, df = 4  | (P = 0.98) | 3); $I^2 = 0$       | 1%            |  |      |   |     |
| Test for overall effect: $Z = 0$        | .65 (P = 0.5 | 51)        |            |                     |               |  |      |   |     |
| 77.4.2 Secondary care                   |              |            |            |                     |               |  |      |   |     |
| Beasley 1993b                           | 28           | 65         | 35         | 71                  | 3.0%          | 0.87 [0.61, 1.26]                      |      | +                                       |     |
| Bremner 1984                            | 16           | 20         | 17         | 20                  | 4.9%          | 0.94 [0.71, 1.25]                      |      | +                                       |     |
| Byerley 1988                            | 14           | 32         | 14         | 34                  | 1.3%          | 1.06 [0.61, 1.86]                      |      |   |     |
| Chiu 1996                               | 12           | 20         | 11         | 20                  | 1.4%          | 1.09 [0.64, 1.86]                      |      |   |     |
| Cohn 1990b                              | 84           | 161        | 40         | 80                  | 5.7%          | 1.04 [0.80, 1.36]                      |      | +                                       |     |
| De Ronchi 1998                          | 16           | 32         | 18         | 33                  | 1.8%          | 0.92 [0.58, 1.46]                      |      |   |     |
| Demyttenaere 1998                       | 22           | 35         | 17         | 31                  | 2.4%          | 1.15 [0.76, 1.72]                      |      | <del>_</del>                            |     |
| Fabre 1991                              | 42           | 103        | 41         | 102                 | 3.6%          | 1.01 [0.73, 1.41]                      |      | +                                       |     |
| Fawcett 1989                            | 9            | 20         | 7          | 20                  | 0.7%          | 1.29 [0.60, 2.77]                      |      |   |     |
| Forlenza 2001                           | 14           | 27         | 14         | 28                  | 1.5%          | 1.04 [0.62, 1.74]                      |      |   |     |
| Geretsegger 1995                        | 18           | 44         | 18         | 47                  | 1.5%          | 1.07 [0.64, 1.77]                      |      |   |     |
| GSK_29060/103                           | 26           | 57         | 22         | 49                  | 2.3%          | 1.02 [0.67, 1.55]                      |      |   |     |
| Keegan 1991                             | 12           | 20         | 16         | 22                  | 2.1%          | 0.82 [0.53, 1.28]                      |      |   |     |
| Laakmann 1988                           | 31           | 63         | 37         | 65                  | 3.7%          | 0.86 [0.62, 1.20]                      |      |   |     |
| Marchesi 1998                           | 40           | 67         | 51         | 75                  | 6.3%          |  |      | _                                       |     |
| MDF/29060/III/070/88/MC                 | 22           | 32         | 12         | 30                  | 1.6%          | 0.88 [0.68, 1.13]                      |      |   |     |
| Moller 1993                             | 53           | 112        | 59         | 110                 | 5.8%          | 1.72 [1.05, 2.82]<br>0.88 [0.68, 1.15] |      | _                                       |     |
| Moller 1998                             | 32           | 81         | 40         | 79                  | 3.3%          | 0.78 [0.55, 1.10]                      |      |   |     |
| Ontiveros Sanchez 1998                  | 7            | 21         | -6         | 21                  | 0.5%          |  |      |   |     |
| Peselow 1989a                           | 17           | 34         | 21         | 32                  |               | 1.17 [0.47, 2.89]                      |      |   |     |
| Peselow 1989b                           | 19           | 40         | 23         | 40                  | 2.3%          | 0.76 [0.50, 1.16]                      |      |   |     |
| Peters 1990                             | 18           | 51         | 23         | 51                  | 1.7%          | 0.83 [0.54, 1.26]<br>0.82 [0.50, 1.33] |      |   |     |
| Reimherr 1990                           | 77           | 149        | 86         | 149                 | 9.3%          |  |      |   |     |
| Staner 1995                             | 7            | 21         | 9          | 19                  | 0.7%          | 0.90 [0.73, 1.10]                      |      |   |     |
|   | 77           | 185        | 85         |                     |               | 0.70 [0.33, 1.52]                      |      |   |     |
| Stark 1985<br>Subtotal (95% CI)         | "            | 1492       | 60         | 186<br>1414         | 7.4%<br>76.8% | 0.91 [0.72, 1.15]<br>0.93 [0.87, 1.00] |      | •                                       |     |
| Total events                            | 713          |            | 721        |                     | . 0.0.0       | one forest month                       |      | 1                                       |     |
| Heterogeneity: Tau <sup>2</sup> = 0.00  |              | 03 4f=     |            | 05)-18              | - 0%          |  |      |   |     |
| Test for overall effect: Z = 1          |              | -          | 24 (1 0    |                     | - 0 70        |  |      |   |     |
| Total (95% CI)                          |              | 2122       |            | 1734                | 100.0%        | 0.96 [0.90, 1.02]                      |      |   |     |
| Total events                            | 1054         |            | 889        |                     |               | ,,                                     |      | 1                                       |     |
| Heterogeneity: Tau <sup>2</sup> = 0.00  |              | 61. df=    |            | 97): I <sup>2</sup> | = 0%          |  |      | + |     |
| Test for overall effect: Z = 1          |              |            | 200 - 0    | //                  |               |  | 0.01 | 0.1 1 10                                | 100 |
| Test for subgroup difference            |              |            | = 1 (P = 0 | 114\ P              | = 54 9%       |  |      | Favours TCA Favours SSRI                |     |
| . Cot for Sabaroup unierent             |              | e.e.e. ul- |            | 47. 1               | - 54.570      |  |      |   |     |

# Primary care versus secondary care subgroup analysis for Comparison 1d. TCAs versus placebo

Figure 59: Depression symptomatology at endpoint

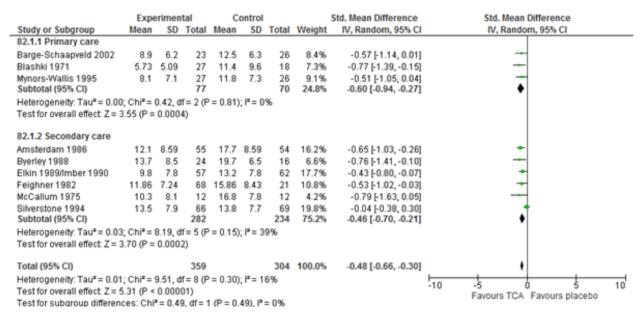


Figure 60: Depression symptomatology change score

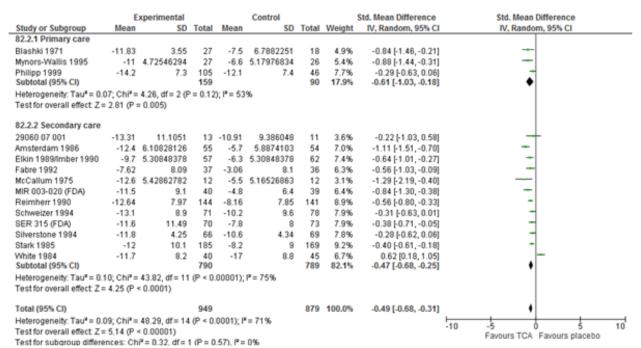


Figure 61: Response

|   | Experim                  | ental     | Contr      | rol                     |        | Risk Ratio          | Risk Ratio                  |
|---|--------------------------|-----------|------------|-------------------------|--------|---------------------|-----------------------------|
| Study or Subgroup                       | Events                   | Total     | Events     | Total                   | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI         |
| 82.4.1 Primary care                     |                          |           |            |                         |        |                     |                             |
| Lecrubier 1997                          | 49                       | 75        | 48         | 76                      | 5.9%   | 1.03 [0.82, 1.31]   | +                           |
| Philipp 1999                            | 70                       | 110       | 29         | 47                      | 5.6%   | 1.03 [0.79, 1.35]   | +                           |
| Schweizer 1998                          | 37                       | 60        | 21         | 60                      | 4.3%   | 1.76 [1.18, 2.62]   | -                           |
| Subtotal (95% CI)                       |                          | 245       |            | 183                     | 15.7%  | 1.19 [0.89, 1.59]   | <b>*</b>                    |
| Total events                            | 156                      |           | 98         |                         |        |                     |                             |
| Heterogeneity: Tau <sup>2</sup> = 0.04; | Chi <sup>2</sup> = 5.98, | df = 2 (  | P = 0.05   | $  \mathbf{l}^2   = 67$ | 7%     |                     |                             |
| Test for overall effect $Z = 1.1$       | 15 (P = 0.25             | 5)        |            |                         |        |                     |                             |
| 82.4.2 Secondary care                   |                          |           |            |                         |        |                     |                             |
| Amsterdam 1986                          | 31                       | 55        | 15         | 54                      | 3.5%   | 2.03 [1.24, 3.31]   |                             |
| Bakish 1992b                            | 34                       | 59        | 20         | 56                      | 4.1%   | 1.61 [1.07, 2.44]   | -                           |
| Bremner 1995                            | 29                       | 50        | 17         | 50                      | 3.8%   | 1.71 [1.08, 2.68]   |                             |
| Byerley 1988                            | 14                       | 34        | 4          | 29                      | 1.3%   | 2.99 [1.10, 8.07]   |                             |
| Cassano 1986                            | 65                       | 165       | 51         | 149                     | 5.3%   | 1.15 [0.86, 1.54]   | -                           |
| Escobar 1980                            | 14                       | 15        | 6          | 12                      | 2.9%   | 1.87 [1.04, 3.34]   |                             |
| Feiger 1996                             | 25                       | 41        | 12         | 40                      | 3.2%   | 2.03 [1.19, 3.46]   |                             |
| Feighner 1982                           | 53                       | 94        | 9          | 45                      | 2.7%   | 2.82 [1.53, 5.19]   |                             |
|   | 8                        | 15        | 5          |                         |        |                     |                             |
| eighner 1989b                           |                          | 45        | _          | 15                      | 1.7%   | 1.60 [0.68, 3.77]   |                             |
| Fontaine 1994                           | 22                       |           | 14         | 45                      | 3.2%   | 1.57 [0.93, 2.66]   |                             |
| Goldberg 1980                           | 27                       | 60        | 27         | 62                      | 4.3%   | 1.03 [0.69, 1.54]   |                             |
| Kusalic 1993                            | 10                       | 13        | 6          | 15                      | 2.3%   | 1.92 [0.97, 3.82]   |                             |
| MIR 003-020 (FDA)                       | 14                       | 43        | . 5        | 43                      | 1.5%   | 2.80 [1.11, 7.09]   |                             |
| Peselow 1989a                           | 21                       | 32        | 14         | 39                      | 3.5%   | 1.83 [1.12, 2.98]   |                             |
| Peselow 1989b                           | 23                       | 40        | 14         | 42                      | 3.4%   | 1.73 [1.04, 2.86]   |                             |
| Reimherr 1990                           | 86                       | 149       | 49         | 150                     | 5.6%   | 1.77 [1.35, 2.31]   | -                           |
| Rickels 1982e                           | 23                       | 51        | 19         | 46                      | 3.8%   | 1.09 [0.69, 1.73]   | _                           |
| Rickels 1991                            | 26                       | 64        | 14         | 67                      | 3.1%   | 1.94 [1.12, 3.38]   |                             |
| Rickels 1995_Study 006-1                | 26                       | 41        | 23         | 36                      | 4.8%   | 0.99 [0.71, 1.39]   |                             |
| Rickels 1995_Study 006-2                | 24                       | 38        | 15         | 42                      | 3.6%   | 1.77 [1.10, 2.84]   | -                           |
| Schweizer 1994                          | 26                       | 73        | 25         | 78                      | 3.9%   | 1.11 [0.71, 1.74]   | +                           |
| Silverstone 1994                        | 33                       | 83        | 35         | 83                      | 4.6%   | 0.94 [0.65, 1.36]   | +                           |
| Smith 1990                              | 24                       | 50        | 12         | 50                      | 3.0%   | 2.00 [1.13, 3.54]   |                             |
| Stark 1985                              | 85                       | 186       | 39         | 169                     | 5.1%   | 1.98 [1.44, 2.72]   | _ <del>-</del>              |
| Subtotal (95% CI)                       |                          | 1496      |            | 1417                    | 84.3%  | 1.57 [1.38, 1.78]   | ♦                           |
| Total events                            | 743                      |           | 450        |                         |        |                     |                             |
| Heterogeneity: Tau <sup>2</sup> = 0.04; | Chi <sup>2</sup> = 42.0  | 0, df = 2 | 3 (P = 0.0 | 009); [2                | = 45%  |                     |                             |
| Test for overall effect: $Z = 6.7$      | 79 (P < 0.00             | 0001)     |            |                         |        |                     |                             |
| Total (95% CI)                          |                          | 1741      |            | 1600                    | 100.0% | 1.51 [1.33, 1.71]   | ◆                           |
| Total events                            | 899                      |           | 548        |                         |        |                     |                             |
| Heterogeneity: Tau <sup>2</sup> = 0.06; |                          | 4. df = 2 |            | 0002): I                | *= 56% |                     |                             |
| Test for overall effect Z = 6.3         |                          | -         | - 6 - 611  |                         |        |                     | 0.01 0.1 1 10 10            |
| est for subgroup difference             |                          |           | 4 (0 - 0   | 000 17-                 | 05.00  |                     | Favours placebo Favours TCA |

# Primary care versus secondary care subgroup analysis for Comparison 1e. Serotonin–norepinephrine reuptake inhibitors (SNRIs) versus SSRIs

Figure 62: Remission

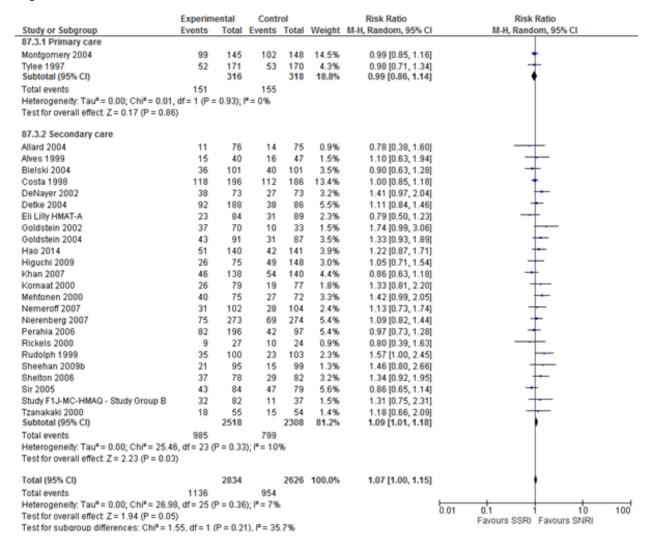
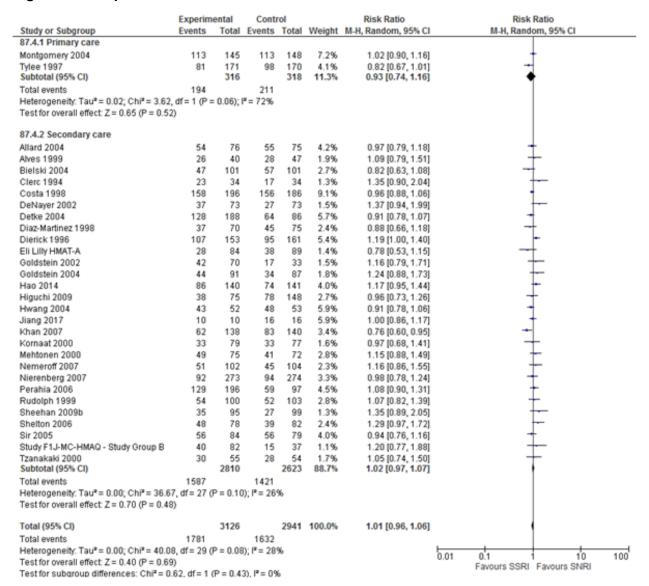
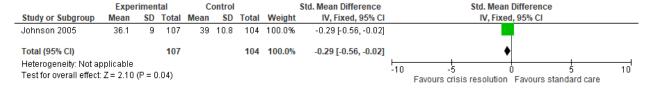


Figure 63: Response



Comparison 2. Crisis resolution team care versus standard care (for adults with non-psychotic severe mental illness)

Figure 64: Mental health symptomatology: Symptom severity (BPRS) 8 weeks after crisis



### Important outcomes

Figure 65: Service utilisation: Admission as inpatient 6 months after crisis

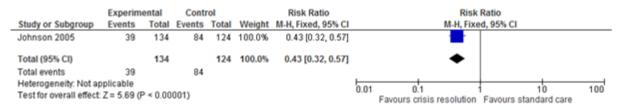


Figure 66: Service utilisation: Bed days in hospital 6 months after crisis

|   | Expe | erimen | tal    | C    | ontrol |       |        | Std. Mean Difference |     | Std. Mear                       | Difference        |                 |    |
|---|------|--------|--------|------|--------|-------|--------|----------------------|-----|---------------------------------|-------------------|-----------------|----|
| Study or Subgroup                                 | Mean | SD     | Total  | Mean | SD     | Total | Weight | IV, Fixed, 95% CI    |     | IV, Fixe                        | d, 95% CI         |                 |    |
| Johnson 2005                                      | 16.1 | 36.5   | 134    | 35   | 47.9   | 123   | 100.0% | -0.45 [-0.69, -0.20] |     |                                 |                   |                 |    |
| Total (95% CI)                                    |      |        | 134    |      |        | 123   | 100.0% | -0.45 [-0.69, -0.20] |     | •                               | •                 |                 |    |
| Heterogeneity: Not ap<br>Test for overall effect: |      |        | .0004) |      |        |       |        |                      | -10 | -5<br>Favours crisis resolution | 0<br>Favours star | 5<br>1dard care | 10 |

Figure 67: Psychological functioning: Quality of life (MANSA) 8 weeks after crisis

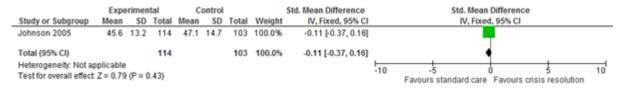


Figure 68: Social functioning: Social functioning (LSP) 8 weeks after crisis

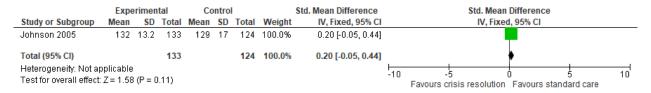


Figure 69: Social functioning: Social functioning (LSP) 6 months after crisis

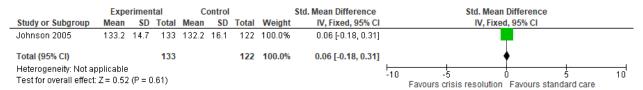
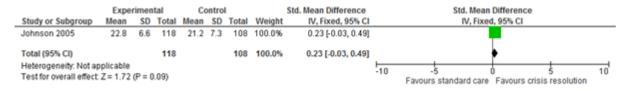


Figure 70: Satisfaction: Patient satisfaction (CSQ-8) 8 weeks after crisis



# Comparison 3. Inpatient versus outpatient settings

# Inpatient versus outpatient settings subgroup analysis for Comparison 3a. Selective serotonin reuptake inhibitors (SSRIs) versus placebo

Figure 71: Depression symptomatology change score

| tudy or Subgroup   |                 | xperimental<br>SD                         | Total     | Moan               | Control                | Total     |              | Std. Mean Difference                                  | Std. Mean Difference |
|--|-----------------|---|-----------|--------------------|------------------------|-----------|--------------|---|----------------------|
| tudy or Subgroup<br>6.1.1 Inpatient  | Mean            | SD  | Total     | Mean               | SD                     | rotal     | Weight       | IV, Random, 95% CI                                    | IV, Random, 95% CI   |
|  | 42.00           | 40.0404                                   | 40        | 40.04              | 0.200040               | 4.4       | 0.500        | 0.24 (4.02 0.04)                                      |                      |
| 9060 07 001  | -13.08          | 10.2191                                   | 99        | -10.91             | 9.386048<br>6.86603233 | 11<br>95  | 0.5%<br>2.2% | -0.21 [-1.03, 0.61]                                   | 1                    |
| Sheehan 2009b<br>Subtotal (95% CI)   | -11.42          | 6.46107963                                | 111       | -11.02             | 0.00003233             | 106       | 2.6%         | -0.06 [-0.34, 0.22]<br>-0.08 [-0.34, 0.19]            | <u> </u>             |
| Heterogeneity: Tau² = 0.00; Chi² = 0.12  | df = 1 /D       | = 0.73\:\IX=00                            |           |                    |                        | 100       | 2.070        | -0.00 [-0.04, 0.10]                                   | 1                    |
| est for overall effect: Z = 0.56 (P = 0.58   |                 | - 0.73), 1 - 0                            | 70        |                    |                        |           |              |   |                      |
| 6.1.2 Outpatient   |                 |   |           |                    |                        |           |              |   |                      |
| 3aune 2018   | -15.96          | 8.58                                      | 52        | -8                 | 8.38                   | 48        | 1.4%         | -0.93 [-1.34, -0.52]                                  |                      |
| Binnemann 2008   | -13.42          | 7.61                                      | 30        | -10.18             | 7.57                   | 31        | 1.0%         | -0.42 [-0.93, 0.09]                                   | <del>-  </del>       |
| Bjerkenstedt 2005  | -8.9            | 8   | 54        | -9.7               | 7                      | 55        | 1.6%         | 0.11 [-0.27, 0.48]                                    | +                    |
| Sumenthal 2007/Hoffman 2011  | -6.1            | 6.7                                       | 49        | -6.1               | 7.3                    | 49        | 1.5%         | 0.00 [-0.40, 0.40]                                    | +                    |
| Bose 2008  | -12.1           | 10.22                                     | 129       | -10.6              | 10.42                  | 134       | 2.5%         | -0.14 [-0.39, 0.10]                                   | +                    |
| Burke 2002   | -12.9           | 9.25                                      | 366       | -9.4               | 9.82                   | 119       | 2.7%         | -0.37 [-0.58, -0.16]                                  | -                    |
| Claghorn 1992a   | -10.72          | 9.39                                      | 32        | -4.59              | 9.35                   | 27        | 1.0%         | -0.65 [-1.17, -0.12]                                  | -                    |
| Claghorn 1992b   | -11.44          | 8.32                                      | 32        | -5.49              | 8.31                   | 27        | 1.0%         | -0.71 [-1.23, -0.18]                                  | -                    |
| layton 2006_study 1  | -14.2           | 8.07                                      | 133       | -12.1              | 7.98                   | 130       | 2.5%         | -0.26 [-0.50, -0.02]                                  | -                    |
| Clayton 2006_study 2   | -12.9           | 8.07                                      | 133       | -11.9              | 7.86                   | 126       | 2.4%         | -0.13 [-0.37, 0.12]                                   | +                    |
| Detke 2004   | -11.7           | 4.61                                      | 85        | -8.8               | 4.82                   | 93        | 2.0%         | -0.61 [-0.91, -0.31]                                  | ~                    |
| Dube 2010  | -15             | 8.82                                      | 54        | -13                | 8.84                   | 122       | 1.9%         | -0.23 [-0.55, 0.10]                                   | +                    |
| Eli Lilly HMAT-A   | -7.4            | 6.44                                      | 87        | -4.78              | 6.42                   | 89        | 2.0%         | -0.41 [-0.70, -0.11]                                  | ~                    |
| Emsley 2018  | -13.6           | 4.70319041                                | 98        | -9.5               | 4.82804308             | 106       | 2.1%         | -0.86 [-1.14, -0.57]                                  | -                    |
| abre 1992  | -9.13           | 8.14                                      | 38        | -3.06              | 8.1                    | 36        | 1.2%         | -0.74 [-1.21, -0.27]                                  | -                    |
| ava 1998a  | -10.95          | 9.41                                      | 109       | -11.6              | 8.9                    | 19        | 1.1%         | 0.07 [-0.42, 0.56]                                    | +                    |
| ava 2005   | -6.3            | 5.38098504                                | 47        | -7.3               | 4.6400431              | 43        | 1.4%         | 0.20 [-0.22, 0.61]                                    | †                    |
| DA 245 (EMD 68 843-010)  | -11.1           | 7.67                                      | 92        | -10.2              | 7.96                   | 99        | 2.1%         | -0.11 [-0.40, 0.17]                                   | †                    |
| orest Laboratories 2000  | -12.95          | 9.89                                      | 243       | -11.2              | 10.35                  | 125       | 2.7%         | -0.17 [-0.39, 0.04]                                   | 7                    |
| orest Research Institute 2005  | -16.26          | 10.37                                     | 266       | -12.4              | 10.34                  | 132       | 2.7%         | -0.37 [-0.58, -0.16]                                  | _                    |
| Folden 2002_448  | -11.89          | 8.19                                      | 206       | -9.9               | 8.04                   | 101       | 2.5%         | -0.24 [-0.48, -0.00]                                  | ٦                    |
| olden 2002_449   | -12.69          | 8.2                                       | 218       | -10.2              | 8.18                   | 110       | 2.6%         | -0.30 [-0.53, -0.07]                                  | 7                    |
| Hunter 2011  | -9.67           | 5.78727915                                | 12        | -8.64              | 5.99548163             | 11        | 0.5%         | -0.17 [-0.99, 0.65]                                   | 7                    |
| lefferson 2000   | -14.7           | 10.56                                     | 296       | -12.1              | 11.05                  | 101       | 2.6%         | -0.24 [-0.47, -0.02]                                  | ]                    |
| Keller 2006_Study 062  | -17.25          | 8.05                                      | 161       | -14                | 8.87                   | 154       | 2.6%         | -0.38 [-0.61, -0.16]                                  |                      |
| Comulainen 2018  | -1.9            | 3.05569959                                | 17        | -2.2               | 3.29146624             | 15        | 0.6%         | 0.09 [-0.60, 0.79]                                    | T                    |
| (ranzler 2006_Group A  | -10.8           | 6.5                                       | 89        | -9.6               | 7.8                    | 100       | 2.1%         | -0.17 [-0.45, 0.12]                                   | l                    |
| am 2016  | -8.8            | 9.9                                       | 31        | -6.5               | 9.6                    | 30        | 1.1%         | -0.23 [-0.74, 0.27]                                   |                      |
| Macias-Cortes 2015   | -8.9            | 2.45051015                                | 46        | -5.7               | 2.46880538             | 43        | 1.2%         | -1.29 [-1.75, -0.83]                                  | ~]                   |
| Mathews 2015   | -15.9           | 10.04                                     | 280       | -13.6              | 10.06                  | 281       | 3.1%         | -0.23 [-0.39, -0.06]                                  | 1                    |
| Ailler 1989a   | -6              | 5.9                                       | 19        | -6.2               | 7.2                    | 22        | 0.8%         | 0.03 [-0.58, 0.64]                                    | J                    |
| Mundt 2012   | -13.4           | 5.7                                       | 55        | -10.7              | 6.6                    | 50        | 1.5%         | -0.44 [-0.82, -0.05]                                  |                      |
| /Y-1042/BRL-029060/CPMS-251  | -10.23          | 7.67                                      | 120       | -8.25              | 7.56                   | 123       | 2.4%         | -0.26 [-0.51, -0.01]                                  | ]                    |
| /Y-1045/BRL-029060/1 (PAR 128)   | -12.39          | 8.77                                      | 694       | -9<br>-07          | 8.63                   | 136       | 3.0%         | -0.39 [-0.57, -0.20]                                  | ]                    |
| Vierenberg 2007  | -7.22           | 6.62                                      | 274       | -5.97              | 6.79                   | 137       | 2.8%         | -0.19 [-0.39, 0.02]                                   | 1                    |
| NKD20006 (NCT00048204)   | -11.1           | 7.9                                       | 117       | -10.9              | 7.8                    | 118       | 2.4%         | -0.03 [-0.28, 0.23]                                   | Ţ                    |
| PAR 01 001 (GSK & FDA)   | -13.36          | 7.93                                      | 172       | -11.33             | 7.93<br>8              | 21        | 0.8%         | -0.25 [-0.85, 0.35]                                   | Ţ                    |
| Rapaport 2009  | -12.11          | 8.02                                      | 173       | -8.85<br>-8.16     |                        | 178       | 2.7%         | -0.41 [-0.62, -0.19]                                  |                      |
| Reimherr 1990  | -11.66          | 8.24                                      | 142       |                    | 7.85                   | 141       | 2.5%         | -0.43 [-0.67, -0.20]                                  | Ţ                    |
| SER 315 (FDA)<br>Stark 1985  | -8.9<br>-11     | 4.52<br>10.1                              | 76<br>185 | -7.8<br>-8.2       | 8                      | 73<br>169 | 1.9%<br>2.7% | -0.17 [-0.49, 0.15]                                   | Ĵ                    |
|  |                 |   |           |                    |                        |           |              | -0.29 [-0.50, -0.08]                                  | <u> </u>             |
| Study 62b (FDA)<br>Study F1J-MC-HMAQ - Study Group B                                   | -8.82<br>-7.63  | 8.71<br>7                                 | 297<br>37 | -5.69<br>-7.1      | 8.65<br>6.96           | 48<br>72  | 2.0%<br>1.5% | -0.36 [-0.66, -0.05]                                  | 1                    |
|  | -7.63<br>-8.1   | 7.6                                       | 326       | -7.1<br>-6.4       | 7.1                    | 329       | 3.2%         | -0.08 [-0.47, 0.32]                                   | _]                   |
| Ollefson 1993/1995   |                 |   | 326<br>80 | -6.4<br>-13.1      | 10.63                  | 329<br>81 |              | -0.23 [-0.38, -0.08]                                  | 1                    |
| /EN XR 367 (FDA)<br>Vade 2002  | -11.26<br>-14.9 | 10.55<br>6.56658206                       | 188       | -13.1              | 6.78196137             | 189       | 2.0%         | 0.17 [-0.14, 0.48]                                    | _[                   |
| vade 2002<br>VELL AK1A4006   | -14.9           | 10.87                                     | 146       | -12.2              | 9.73                   | 148       | 2.6%         | -0.43 [-0.64, -0.23]<br>-0.16 [-0.39, 0.06]           | <u> </u>             |
| VELL AKTA4006<br>Vernicke 1987   | -13.9           | 8.67                                      | 297       | -12.2              | 9.73                   | 48        | 2.0%         |   |                      |
| Vernicke 1987<br>Vernicke 1988   | -8.83           | 8.67                                      | 183       | -5. <i>1</i><br>-7 | 8.6                    | 48<br>77  | 2.0%         | -0.36 [-0.67, -0.05]<br>-0.43 [-0.70, -0.16]          |                      |
| Subtotal (95% CI)  | -10.0           | 0.3                                       | 6916      | -7                 | 0.0                    | 4716      | 97.4%        | -0.43 [-0.70, -0.16]<br>- <b>0.29 [-0.36, -0.23</b> ] |                      |
| Heterogeneity: Tau² = 0.02; Chi² = 105.<br>Fest for overall effect: Z = 9.46 (P < 0.00 |                 | 8 (P < 0.00001                            |           | 54%                |                        |           |              | 5.25 [ 5100] -0120]                                   |                      |
|  | 2001)           |   | 7027      |                    |                        | 4022      | 100.0%       | 0.301035 0.331  |                      |
| <b>「otal (95% CI)</b><br>Heterogeneity: Tau² = 0.02; Chi² = 107.                       | 01.46.5         | 0 /D ~ 0 00001                            |           | - 40/              |                        | 4022      | 100.0%       | -0.29 [-0.35, -0.23]                                  | <u>'</u>             |
|  |                 | 0 7 P P D D D D D D D D D D D D D D D D D | 1: P = 6  | v 196              |                        |           |              |   | -10 -5 0 5           |

Figure 72: Response

| Study or Subgroup  | Experim<br>Events |            | Contr<br>Events |            | Weight       | Risk Ratio<br>M-H, Random, 95% CI      | Risk Ratio<br>M-H, Random, 95% CI |
|--|-------------------|------------|-----------------|------------|--------------|--|-----------------------------------|
| 76.2.1 Inpatient   |                   |            |                 |            |              |  |                                   |
| Katz 2004  | 11                | 28         | 6               | 25         | 0.4%         | 1.64 [0.71, 3.78]                      | +                                 |
| Sheehan 2009b  | 27                | 99         | 23              | 95         | 1.0%         | 1.13 [0.70, 1.82]                      |                                   |
| Subtotal (95% CI)  |                   | 127        |                 | 120        | 1.4%         | 1.24 [0.82, 1.87]                      | <b>—</b>                          |
| Total events   | 38                | 0.45\-0    | 29              |            |              |  |                                   |
| Heterogeneity: Tau² = 0.00; Chi² = 0.58<br>Test for overall effect: Z = 1.00 (P = 0.32 |                   | : 0.45); i | ·= U%           |            |              |  |                                   |
| 76.2.2 Outpatient  |                   |            |                 |            |              |  |                                   |
| 3innemann 2008   | 25                | 43         | 17              | 39         | 1.1%         | 1.33 [0.86, 2.07]                      | <del> </del>                      |
| Bjerkenstedt 2005  | 20                | 57         | 21              | 58         | 0.9%         | 0.97 [0.59, 1.58]                      | +                                 |
| 3ose 2008  | 59                | 132        | 51              | 135        | 2.0%         | 1.18 [0.89, 1.58]                      | +                                 |
| Burke 2002   | 179               | 379        | 33              | 127        | 1.8%         | 1.82 [1.33, 2.48]                      | -                                 |
| Byerley 1988   | 14                | 32         | 4               | 29         | 0.3%         | 3.17 [1.18, 8.55]                      |                                   |
| Claghorn 1992b   | 15                | 36         | 6               | 36         | 0.4%         | 2.50 [1.09, 5.71]                      |                                   |
| Clayton 2006_study 1   | 90                | 142        | 69              | 141        | 2.8%         | 1.30 [1.05, 1.60]                      |                                   |
| Clayton 2006_study 2   | 82<br>64          | 149<br>86  | 64<br>41        | 137<br>93  | 2.6%         | 1.18 [0.94, 1.48]                      |                                   |
| Detke 2004<br>Doogan 1994  | 50                | 99         | 40              | 101        | 2.3%<br>1.9% | 1.69 [1.30, 2.19]<br>1.28 [0.94, 1.74] | _                                 |
| Dube 2010  | 29                | 62         | 59              | 138        | 1.7%         | 1.09 [0.79, 1.52]                      | <del> </del>                      |
| Dunbar 1993  | 72                | 170        | 30              | 171        | 1.5%         | 2.41 [1.67, 3.49]                      | <del></del>                       |
| Eli Lilly HMAT-A   | 38                | 89         | 24              | 90         | 1.2%         | 1.60 [1.05, 2.43]                      | <del></del>                       |
| Emsley 2018  | 54                | 99         | 36              | 107        | 1.8%         | 1.62 [1.18, 2.24]                      |                                   |
| Fava 1998a   | 63                | 109        | 10              | 19         | 1.1%         | 1.10 [0.70, 1.73]                      | +                                 |
| Forest Laboratories 2000   | 118               | 257        | 51              | 129        | 2.4%         | 1.16 [0.90, 1.49]                      | +                                 |
| Forest Research Institute 2005   | 162               | 274        | 56              | 135        | 2.7%         | 1.43 [1.14, 1.78]                      | -                                 |
| Goldstein 2002   | 17                | 33         | 33              | 70         | 1.2%         | 1.09 [0.72, 1.65]                      | +                                 |
| Goldstein 2004   | 34                | 87         | 27              | 89         | 1.3%         | 1.29 [0.86, 1.94]                      | <del> </del>                      |
| Gual 2003  | 19                | 44         | 15              | 39         | 0.9%         | 1.12 [0.67, 1.89]                      |                                   |
| Hirayasu 2011a   | 133               | 205        | 66              | 105        | 3.2%         | 1.03 [0.86, 1.23]                      | <u> </u>                          |
| Hirayasu 2011b   | 179               | 361        | 45              | 124        | 2.3%         | 1.37 [1.06, 1.76]                      | <u></u>                           |
| Hunter 2010_study 1<br>Hunter 2011   | 6<br>6            | 14<br>13   | 6<br>6          | 14<br>11   | 0.4%         | 1.00 [0.43, 2.35]<br>0.85 [0.38, 1.88] |                                   |
| Jefferson 2000   | 145               | 310        | 36              | 105        | 2.0%         | 1.36 [1.02, 1.82]                      | _                                 |
| Kramer 1998  | 33                | 72         | 20              | 70         | 1.1%         | 1.60 [1.03, 2.51]                      | <del></del>                       |
| Kranzler 2006_Group A  | 33                | 89         | 26              | 100        | 1.2%         | 1.43 [0.93, 2.19]                      | <del> </del>                      |
| Lam 2016   | 9                 | 31         | 10              | 30         | 0.5%         | 0.87 [0.41, 1.84]                      | <del></del>                       |
| Lepola 2003  | 183               | 315        | 74              | 154        | 3.1%         | 1.21 [1.00, 1.46]                      | <del>-</del>                      |
| Macias-Cortes 2015   | 19                | 46         | 5               | 43         | 0.3%         | 3.55 [1.45, 8.68]                      | <del></del>                       |
| Mathews 2015   | 176               | 289        | 142             | 290        | 3.6%         | 1.24 [1.07, 1.44]                      | +                                 |
| Mendels 1999   | 37                | 89         | 24              | 91         | 1.2%         | 1.58 [1.03, 2.41]                      |                                   |
| Mundt 2012   | 33                | 80         | 20              | 85         | 1.0%         | 1.75 [1.10, 2.79]                      |                                   |
| MY-1042/BRL-029060/CPMS-251  | 56                | 125        | 44              | 129        | 1.9%         | 1.31 [0.96, 1.79]                      | <u> </u>                          |
| MY-1045/BRL-029060/1 (PAR 128)   | 461               | 708        | 69              | 140        | 3.3%         | 1.32 [1.11, 1.58]                      |                                   |
| Nemeroff 2007  | 45                | 104        | 37              | 102        | 1.7%         | 1.19 [0.85, 1.67]                      |                                   |
| Nierenberg 2007  | 94                | 274        | 36              | 137        | 1.7%         | 1.31 [0.94, 1.81]                      | $\Gamma$                          |
| NKD20006 (NCT00048204)   | 57<br>71          | 125<br>129 | 59<br>45        | 125<br>129 | 2.2%         | 0.97 [0.74, 1.26]<br>1.58 [1.19, 2.09] | ]_                                |
| Olie 1997<br>PAR 01 001 (GSK & FDA)  | 11                | 25         | 8               | 25         | 2.1%<br>0.5% | 1.38 [0.67, 2.83]                      |                                   |
| Perahia 2006   | 59                | 97         | 51              | 99         | 2.4%         | 1.18 [0.92, 1.51]                      | <del> -</del>                     |
| Peselow 1989a  | 17                | 34         | 14              | 39         | 0.8%         | 1.39 [0.81, 2.38]                      | <del> </del>                      |
| Peselow 1989b  | 19                | 40         | 14              | 42         | 0.8%         | 1.43 [0.83, 2.44]                      | +-                                |
| Rapaport 2009  | 100               | 177        | 71              | 180        | 2.7%         | 1.43 [1.15, 1.79]                      | <del></del>                       |
| Ratti 2011_study 096   | 65                | 113        | 73              | 123        | 2.8%         | 0.97 [0.78, 1.20]                      | +                                 |
| Ravindran 1995   | 17                | 40         | 7               | 26         | 0.5%         | 1.58 [0.76, 3.27]                      | +                                 |
| Reimherr 1990  | 77                | 149        | 49              | 150        | 2.1%         | 1.58 [1.20, 2.09]                      |                                   |
| Rickels 1992   | 22                | 55         | 10              | 56         | 0.6%         | 2.24 [1.17, 4.28]                      |                                   |
| Roose 2004   | 32                | 84         | 34              | 90         | 1.4%         | 1.01 [0.69, 1.47]                      | +                                 |
| Rudolph 1999   | 52                | 103        | 41              | 98         | 1.9%         | 1.21 [0.89, 1.63]                      | <del> </del>                      |
| Smith 1992   | 15                | 39         | 8               | 38         | 0.5%         | 1.83 [0.88, 3.80]                      | <del></del>                       |
| Stark 1985   | 77                | 185        | 39              | 169        | 1.8%         | 1.80 [1.30, 2.49]                      | -                                 |
| Study F1J-MC-HMAQ - Study Group B  | 15                | 37         | 28              | 75         | 1.0%         | 1.09 [0.67, 1.77]                      |                                   |
| Tollefson 1993/1995  | 121               | 336        | 90              | 335        | 2.6%         | 1.34 [1.07, 1.68]                      |                                   |
| Valle-Cabrera 2018<br>Wade 2002  | 28<br>103         | 39<br>191  | 12<br>79        | 38<br>189  | 0.9%         | 2.27 [1.37, 3.78]                      | _                                 |
| Wade 2002<br>Wang 2014c  | 91                | 157        | 79<br>78        | 157        | 2.8%<br>2.9% | 1.29 [1.04, 1.60]<br>1.17 [0.95, 1.43] | <u> </u>                          |
| WELL AK1A4006  | 88                | 155        | 78              | 154        | 2.9%         | 1.12 [0.91, 1.38]                      | <del> </del>                      |
| Wernicke 1987  | 112               | 308        | 9               | 48         | 0.7%         | 1.94 [1.06, 3.56]                      | <u> </u>                          |
| Wernicke 1988  | 89                | 189        | 18              | 78         | 1.2%         | 2.04 [1.32, 3.14]                      | <del></del>                       |
| Subtotal (95% CI)  |                   | 8311       |                 | 6076       | 98.6%        | 1.33 [1.26, 1.40]                      | I+                                |
| Total events   | 4190              |            | 2268            |            |              | ,                                      |                                   |
| Heterogeneity: Tau² = 0.01; Chi² = 95.5<br>Test for overall effect: Z = 10.33 (P < 0.0 | D, df = 59 (l     | P = 0.00   |                 | 3%         |              |  |                                   |
| Total (95% CI)   | ,                 | 8438       |                 | 6196       | 100.0%       | 1.33 [1.26, 1.40]                      |                                   |
| Total events   | 4228              |            | 2297            |            |              | 2,                                     | ľ                                 |
| Heterogeneity: Tau² = 0.01; Chi² = 96.0  |                   | P = 0.00   |                 | 7%         |              |  |                                   |
| Fest for overall effect: Z = 10.46 (P < 0.0  |                   | 2.00       | ,,              |            |              |  | 0.01 0.1 1 10 1                   |

# Inpatient versus outpatient settings subgroup analysis for Comparison 3b. SSRIs versus tricyclic antidepressants (TCAs)

Figure 73: Depression symptomatology endpoint

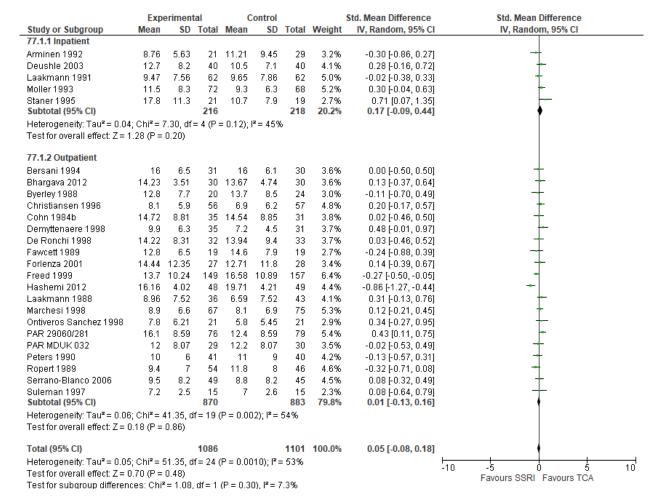


Figure 74: Depression symptomatology change score

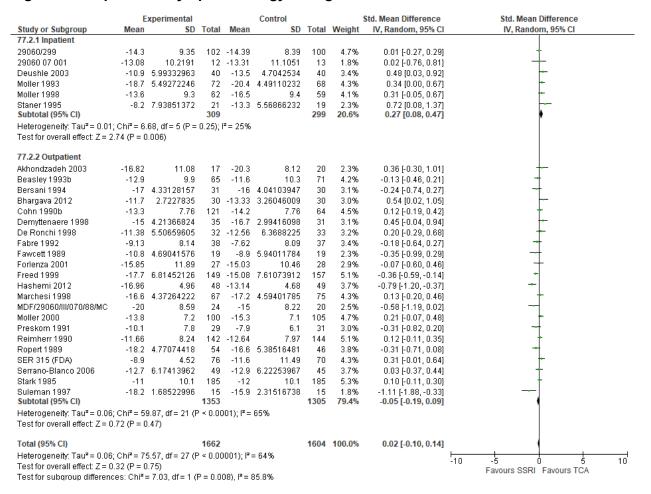


Figure 75: Remission

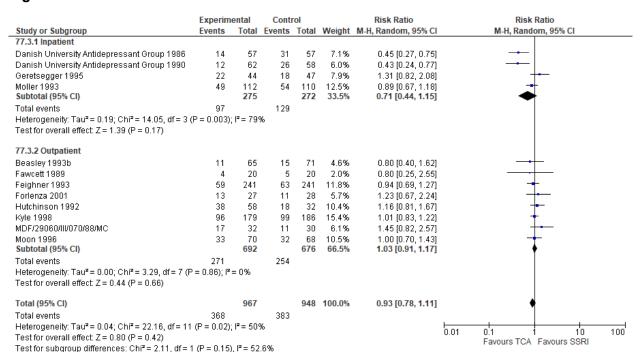
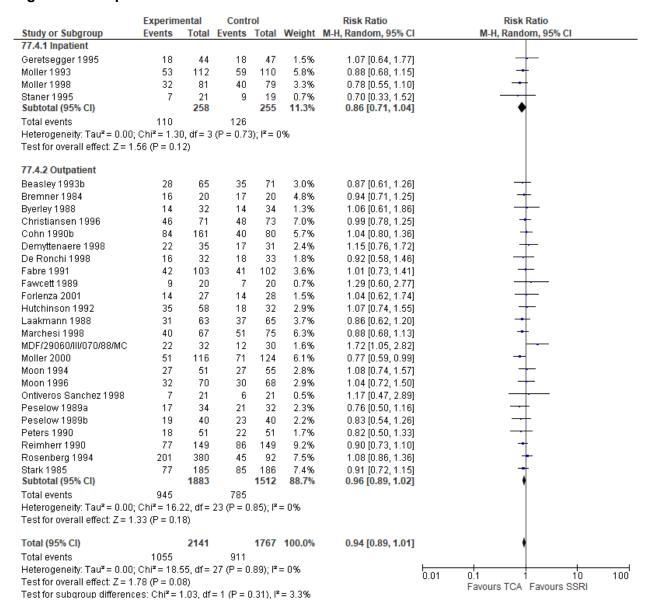
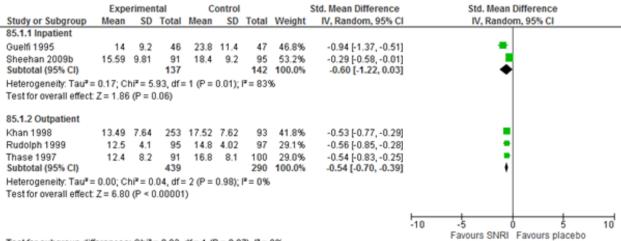


Figure 76: Response



Inpatient versus outpatient settings subgroup analysis for Comparison 3c. Serotonin–norepinephrine reuptake inhibitors (SNRIs) versus placebo

Figure 77: Depression symptomatology endpoint

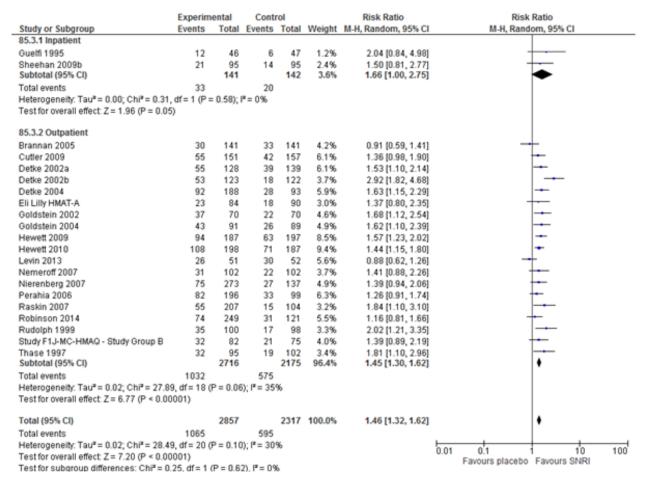


Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%

Figure 78: Depression symptomatology change score

|   |             | xperimental             |         |        | Control    |       |        | Std. Mean Difference | Std. Mean Difference                          |
|---|-------------|-------------------------|---------|--------|------------|-------|--------|----------------------|---|
| Study or Subgroup                           | Mean        | SD                      | Total   | Mean   | SD         | Total | Weight | IV, Random, 95% CI   | IV, Random, 95% CI                            |
| 85.2.1 Inpatient                            |             |                         |         |        |            |       |        |                      |   |
| Guelfi 1995                                 | -14.2       | 9.6                     | 46      | -4.8   | 11         | 47    | 3.9%   | -0.90 [-1.33, -0.47] | -   |
| Sheehan 2009b                               | -14.3       | 7.32900744              | 91      | -11.02 | 6.86603233 | 95    | 6.2%   | -0.46 [-0.75, -0.17] | <u>.</u>                                      |
| Subtotal (95% CI)                           |             |                         | 137     |        |            | 142   | 10.1%  | -0.65 [-1.08, -0.22] | •   |
| Heterogeneity: Tau* = 0.06; Chi* = 2.80     | , df = 1 (P | $= 0.09$ ); $I^{a} = 6$ | 4%      |        |            |       |        |                      |   |
| Test for overall effect: Z = 2.98 (P = 0.0) | 03)         |                         |         |        |            |       |        |                      |   |
| 85.2.2 Outpatient                           |             |                         |         |        |            |       |        |                      |   |
| Brannan 2005                                | -10.85      | 7.93                    | 132     | -10.27 | 7.81       | 136   | 7.5%   | -0.07 (-0.31, 0.17)  | +   |
| Detke 2004                                  | -11.55      | 4.84                    | 186     | -8.8   | 4.82       | 93    | 7.2%   | -0.57 [-0.82, -0.31] | +   |
| Eli Lilly HMAT-A                            | -6.31       | 6.3                     | 81      | -4.78  | 6.42       | 89    | 6.0%   | -0.24 [-0.54, 0.06]  | -   |
| Hewett 2010                                 | -17         | 10.56                   | 193     | -13.2  | 10.64      | 186   | 8.6%   | -0.36 [-0.56, -0.15] | •   |
| Higuchi 2016                                | -15.17      | 10.08                   | 348     | -12.41 | 10.12      | 182   | 9.3%   | -0.27 [-0.45, -0.09] | -   |
| Mendels 1993                                | -14.8       | 9.64                    | 77      | -10.53 | 8.98       | 75    | 5.6%   | -0.46 [-0.78, -0.13] | -   |
| Nierenberg 2007                             | -7.61       | 6.94                    | 273     | -5.97  | 6.79       | 137   | 8.5%   | -0.24 [-0.44, -0.03] | +   |
| Robinson 2014                               | -7.42       | 7.37                    | 201     | -7.15  | 7.51       | 95    | 7.4%   | -0.04 [-0.28, 0.21]  | +   |
| Schweizer 1994                              | -15.6       | 9.8                     | 64      | -10.2  | 9.6        | 78    | 5.3%   | -0.55 [-0.89, -0.22] | +   |
| Study F1J-MC-HMAQ - Study Group B           | -8          | 6.75                    | 81      | -7.1   | 6.96       | 72    | 5.7%   | -0.13 [-0.45, 0.19]  | +   |
| VEN 600A-303 (FDA)                          | -10.14      | 8.45                    | 69      | -9.89  | 8.45       | 79    | 5.6%   | -0.03 [-0.35, 0.29]  | †   |
| VEN 600A-313 (FDA)                          | -11.39      | 8.39                    | 149     | -9.49  | 8.2        | 75    | 6.5%   | -0.23 [-0.51, 0.05]  | *   |
| VEN XR 367 (FDA)                            | -15.13      | 10.65                   | 157     | -13.1  | 10.63      | 81    | 6.8%   | -0.19 [-0.46, 0.08]  |   |
| Subtotal (95% CI)                           |             |                         | 2011    |        |            | 1378  | 89.9%  | -0.26 [-0.35, -0.17] | 1   |
| Heterogeneity: Tau* = 0.01; Chi* = 19.4     | 3, df = 12  | (P = 0.08); P =         | 38%     |        |            |       |        |                      |   |
| Test for overall effect: Z = 5.53 (P < 0.0) | 0001)       |                         |         |        |            |       |        |                      |   |
| Total (95% CI)                              |             |                         | 2148    |        |            | 1520  | 100.0% | -0.29 [-0.39, -0.19] | 4   |
| Heterogeneity: Tau* = 0.02; Chi* = 29.4     | 4, df = 14  | (P = 0.009); P          | = 52%   |        |            |       |        |                      | -10 -5 0 5 10                                 |
| Test for overall effect Z = 5.77 (P < 0.0)  | 0001)       |                         |         |        |            |       |        |                      | -10 -5 0 5 10<br>Favours SNRI Favours placebo |
| Test for subgroup differences: Chi* = 3     | 12, df = 1  | (P = 0.08), P           | = 68.09 | 6      |            |       |        |                      | rations district Payouts placedo              |

Figure 79: Remission



Inpatient versus outpatient settings subgroup analysis for Comparison 3d. SNRIs versus SSRIs

Figure 80: Depression symptomatology endpoint

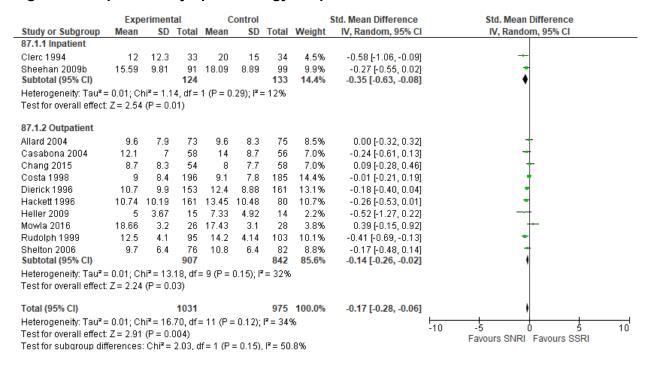


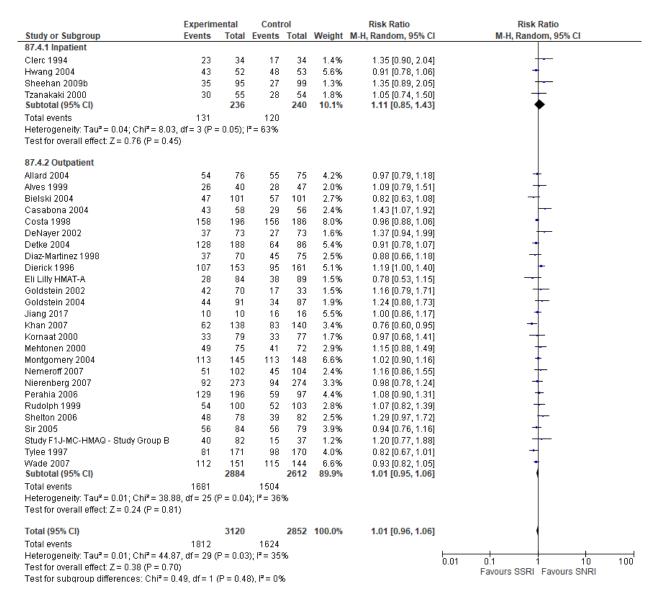
Figure 81: Depression symptomatology change score

|  | E           | xperimental                  |        |        | Control    |       |        | Std. Mean Difference | Std. Mean Difference                       |
|--|-------------|------------------------------|--------|--------|------------|-------|--------|----------------------|--|
| Study or Subgroup  | Mean        | SD.                          | Total  | Mean   | SD         | Total | Weight | IV, Random, 95% CI   | IV, Random, 95% CI                         |
| 87.2.1 Inpatient   |             |                              |        |        |            |       |        |                      |  |
| Clerc 1994   | -22.8       | 9.16733331                   | 33     | -15.7  | 11.7260394 | 34    | 3.3%   | -0.67 [-1.16, -0.17] |  |
| Sheehan 2009b  | -14.3       | 7.32900744                   | 91     | -11.42 | 6.46107963 | 99    | 6.1%   | -0.42 [-0.70, -0.13] | -  |
| Subtotal (95% CI)  |             |                              | 124    |        |            | 133   | 9.4%   | -0.48 [-0.73, -0.23] | <b>♦</b>                                   |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.73,                       | df = 1 (P   | r = 0.39); $r = 0$           | %      |        |            |       |        |                      |  |
| Test for overall effect: Z = 3.78 (P = 0.00  | 002)        |                              |        |        |            |       |        |                      |  |
| 87.2.2 Outpatient  |             |                              |        |        |            |       |        |                      |  |
| Allard 2004  | -18         | 5.71926569                   | 73     | -17.4  | 6.08522802 | 75    | 5.5%   | -0.10 [-0.42, 0.22]  | -  |
| Bielski 2004   | -13.6       | 9.6                          | 98     | -15.9  | 10.3       | 97    | 6.2%   | 0.23 [-0.05, 0.51]   | +  |
| Chang 2015   | -17.2       | 5.49454275                   | 54     | -16.3  | 5.09362347 | 58    | 4.7%   | -0.17 [-0.54, 0.20]  | -+   |
| Costa 1998   | -21.4       | 5.5569776                    | 196    | -20.6  | 5.18844871 | 185   | 7.8%   | -0.15 [-0.35, 0.05]  | +  |
| DeNayer 2002   | -14.4       | 7.6                          | 64     | -10.4  | 8.6        | 67    | 5.1%   | -0.49 [-0.84, -0.14] | <del>-</del>                               |
| Detke 2004   | -11.55      | 4.84                         | 186    | -11.7  | 4.61       | 85    | 6.7%   | 0.03 [-0.23, 0.29]   | +  |
| Dierick 1996   | -16.3       | 7.29931504                   | 153    | -14.2  | 6.40721468 | 161   | 7.4%   | -0.31 [-0.53, -0.08] | -  |
| Eli Lilly HMAT-A   | -6.31       | 6.3                          | 81     | -7.4   | 6.44       | 87    | 5.8%   | 0.17 [-0.13, 0.47]   | +  |
| Heller 2009  | -15.07      | 2.55984374                   | 15     | -14.03 | 3.39863208 | 14    | 1.8%   | -0.34 [-1.07, 0.40]  | +  |
| Khan 2007  | -19.3       | 9.1                          | 91     | -19.2  | 8.6        | 110   | 6.3%   | -0.01 [-0.29, 0.27]  | +  |
| Mowla 2016   | -9.3        | 2.48394847                   | 26     | -9.97  | 2.5855367  | 28    | 2.9%   | 0.26 [-0.28, 0.80]   | +  |
| Nierenberg 2007  | -7.61       | 6.94                         | 273    | -7.22  | 6.62       | 274   | 8.6%   | -0.06 [-0.23, 0.11]  | †  |
| Shelton 2006   | -12.7       | 4.6400431                    | 76     | -11.3  | 4.6400431  | 82    | 5.6%   | -0.30 [-0.61, 0.01]  | -  |
| Sir 2005   | -14.3       | 8.35                         | 79     | -15.9  | 8.44       | 79    | 5.6%   | 0.19 [-0.12, 0.50]   | †  |
| Study F1J-MC-HMAQ - Study Group B  | -8          | 6.75                         | 81     | -7.63  | 7          | 37    | 4.5%   | -0.05 [-0.44, 0.34]  | +  |
| VEN XR 367 (FDA)   | -15.13      | 10.65                        |        | -11.26 | 10.55      | 80    | 6.4%   | -0.36 [-0.63, -0.09] | <del>-</del>                               |
| Subtotal (95% CI)  |             |                              | 1703   |        |            | 1519  | 90.6%  | -0.09 [-0.19, 0.01]  |  |
| Heterogeneity: Tau² = 0.02; Chi² = 29.0<br>Test for overall effect: Z = 1.73 (P = 0.08 |             | (P = 0.02); l <sup>2</sup> = | = 48%  |        |            |       |        |                      |  |
| Total (95% CI)   |             |                              | 1827   |        |            | 1652  | 100.0% | -0.13 [-0.24, -0.02] | •  |
| Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 38.3                        | 6, df = 17  | $(P = 0.002); I^2$           | = 56%  |        |            |       |        |                      | -10 -5 0 5 10                              |
| Test for overall effect: $Z = 2.36$ (P = 0.02  | 2)          |                              |        |        |            |       |        |                      | -10 -5 0 5 10<br>Favours SNRI Favours SSRI |
| Test for subgroup differences: Chi₹ = 8.   | .03, df = 1 | I (P = 0.005), I             | = 87.5 | i%     |            |       |        |                      | FAVOUIS SINKI FAVOUIS SSKI                 |

Figure 82: Remission

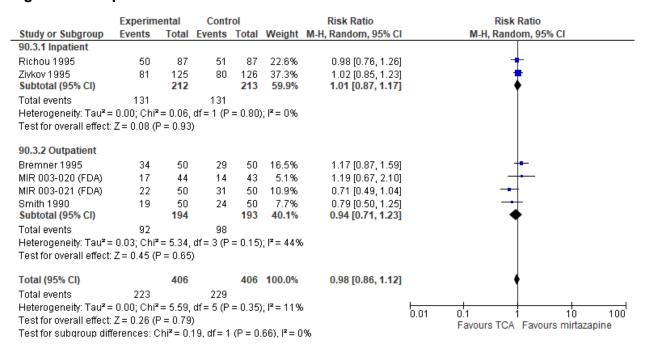
|   | Experim      | ental     | Contr                    | rol   |        | Risk Ratio          | Risk Ratio                |
|---|--------------|-----------|--------------------------|-------|--------|---------------------|---------------------------|
| Study or Subgroup   | Events       | Total     | <b>Events</b>            | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI       |
| 87.3.1 Inpatient  |              |           |                          |       |        |                     |                           |
| Sheehan 2009b   | 21           | 95        | 15                       | 99    | 1.3%   | 1.46 [0.80, 2.66]   | <del>  -</del>            |
| Tzanakaki 2000  | 18           | 55        | 15                       | 54    | 1.4%   | 1.18 [0.66, 2.09]   | <del></del>               |
| Subtotal (95% CI)   |              | 150       |                          | 153   | 2.7%   | 1.30 [0.86, 1.97]   | <b>◆</b>                  |
| Total events  | 39           |           | 30                       |       |        |                     |                           |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.26 | df=1 (P=     | = 0.61);  | l² = 0%                  |       |        |                     |                           |
| Test for overall effect: Z = 1.26 (P = 0.21                     | )            |           |                          |       |        |                     |                           |
| 87.3.2 Outpatient   |              |           |                          |       |        |                     |                           |
| Allard 2004   | 11           | 76        | 14                       | 75    | 0.9%   | 0.78 [0.38, 1.60]   | <del></del>               |
| Alves 1999  | 15           | 40        | 16                       | 47    | 1.4%   | 1.10 [0.63, 1.94]   | <del></del>               |
| Bielski 2004  | 36           | 101       | 40                       | 101   | 3.4%   | 0.90 [0.63, 1.28]   | <del>-</del>              |
| Casabona 2004   | 18           | 58        | 20                       | 56    | 1.7%   | 0.87 [0.52, 1.46]   | <del></del>               |
| Costa 1998  | 118          | 196       | 112                      | 186   | 11.4%  | 1.00 [0.85, 1.18]   | +                         |
| DeNayer 2002  | 38           | 73        | 27                       | 73    | 3.1%   | 1.41 [0.97, 2.04]   | <del> </del>              |
| Detke 2004  | 92           | 188       | 38                       | 86    | 5.1%   | 1.11 [0.84, 1.46]   | +                         |
| Eli Lilly HMAT-A  | 23           | 84        | 31                       | 89    | 2.2%   | 0.79 [0.50, 1.23]   | <del></del>               |
| Goldstein 2002  | 37           | 70        | 10                       | 33    | 1.4%   | 1.74 [0.99, 3.06]   | <del></del>               |
| Goldstein 2004  | 43           | 91        | 31                       | 87    | 3.4%   | 1.33 [0.93, 1.89]   | <del> </del>              |
| Khan 2007   | 46           | 138       | 54                       | 140   | 4.2%   | 0.86 [0.63, 1.18]   | <del></del>               |
| Kornaat 2000  | 26           | 79        | 19                       | 77    | 1.8%   | 1.33 [0.81, 2.20]   | +-                        |
| Mehtonen 2000   | 40           | 75        | 27                       | 72    | 3.2%   | 1.42 [0.99, 2.05]   | <del> </del>              |
| Montgomery 2004   | 99           | 145       | 102                      | 148   | 12.2%  | 0.99 [0.85, 1.16]   | +                         |
| Nemeroff 2007   | 31           | 102       | 28                       | 104   | 2.4%   | 1.13 [0.73, 1.74]   | +                         |
| Nierenberg 2007   | 75           | 273       | 69                       | 274   | 5.1%   | 1.09 [0.82, 1.44]   | +                         |
| Perahia 2006  | 82           | 196       | 42                       | 97    | 5.1%   | 0.97 [0.73, 1.28]   | +                         |
| Rickels 2000  | 9            | 27        | 10                       | 24    | 0.9%   | 0.80 [0.39, 1.63]   | <del></del>               |
| Rudolph 1999  | 35           | 100       | 23                       | 103   | 2.2%   | 1.57 [1.00, 2.45]   | <del></del>               |
| Shelton 2006  | 37           | 78        | 29                       | 82    | 3.1%   | 1.34 [0.92, 1.95]   | <del> </del>              |
| Sir 2005  | 43           | 84        | 47                       | 79    | 5.2%   | 0.86 [0.65, 1.14]   | <del></del>               |
| Study F1J-MC-HMAQ - Study Group B                               | 32           | 82        | 11                       | 37    | 1.4%   | 1.31 [0.75, 2.31]   | <del> </del>              |
| Tylee 1997  | 52           | 171       | 53                       | 170   | 4.1%   | 0.98 [0.71, 1.34]   | +                         |
| Wade 2007   | 102          | 151       | 103                      | 144   | 12.6%  | 0.94 [0.81, 1.10]   | +                         |
| Subtotal (95% CI)   |              | 2678      |                          | 2384  | 97.3%  | 1.04 [0.97, 1.12]   | <b>)</b>                  |
| Total events  | 1140         |           | 956                      |       |        |                     |                           |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 27.2 | 2, df = 23 ( | P = 0.25  | 5); I <sup>2</sup> = 15° | %     |        |                     |                           |
| Test for overall effect: Z = 1.19 (P = 0.23                     | 3)           |           |                          |       |        |                     |                           |
| Total (95% CI)  |              | 2828      |                          | 2537  | 100.0% | 1.05 [0.98, 1.12]   |                           |
| Total events  | 1179         |           | 986                      |       |        |                     |                           |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 28.7 |              | P = 0.27  |                          | %     |        |                     |                           |
| Test for overall effect: Z = 1.36 (P = 0.17                     |              |           | ,,. ,.                   |       |        |                     | 0.01 0.1 1 10 100         |
| Test for subgroup differences: Chi <sup>2</sup> = 1             |              | (P = 0.3) | 0), $ \mathbf{r} = 7.4$  | 1%    |        |                     | Favours SSRI Favours SNRI |
|   | ,            | ,. 0.0    |                          |       |        |                     |                           |

Figure 83: Response



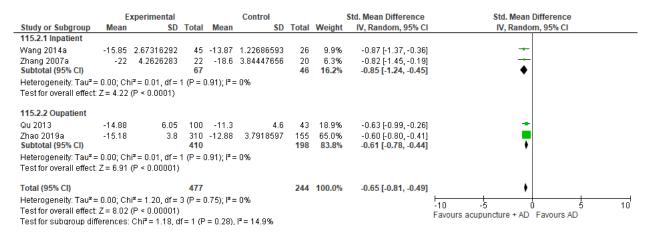
Inpatient versus outpatient settings subgroup analysis for Comparison 3e. Mirtazapine versus TCAs

Figure 84: Response



Inpatient versus outpatient settings subgroup analysis for Comparison 3f. Acupuncture + antidepressants versus antidepressants

Figure 85: Depression symptomatology change score



# Comparison 4. Acute psychiatric day hospital care versus inpatient care (for adults with depression and non-psychotic severe mental illness)

Figure 86: Psychiatric symptom severity at 2-3 months post-admission

|   | E     | cperimental | I     |           | Control    |       |        | Std. Mean Difference | Std. Mean Difference                                    |
|---|-------|-------------|-------|-----------|------------|-------|--------|----------------------|---|
| Study or Subgroup                                 | Mean  | SD          | Total | Mean      | SD         | Total | Weight | IV, Random, 95% CI   | IV, Random, 95% CI                                      |
| Creed 1997  | -15.6 | 7.949333    | 63    | -14.8     | 5.903203   | 60    | 30.4%  | -0.11 [-0.47, 0.24]  | +   |
| Dinger 2014                                       | -7.2  | 4.43044     | 23    | -6.3      | 4.603211   | 18    | 15.0%  | -0.20 [-0.81, 0.42]  | <del></del>   |
| Kallert 2007                                      | -0.43 | 0.304631    | 596   | -0.5      | 0.344529   | 521   | 54.6%  | 0.22 [0.10, 0.33]    | •   |
| Total (95% CI)                                    |       |             | 682   |           |            | 599   | 100.0% | 0.05 [-0.22, 0.33]   | •   |
| Heterogeneity: Tau² =<br>Test for overall effect: |       |             | ,     | 9 = 0.11) | ); I²= 54% |       |        |                      | -10 -5 0 5 10 Favours acute day hosp. Favours inpatient |

Figure 87: Psychiatric symptom severity at 12-14 months post-admission

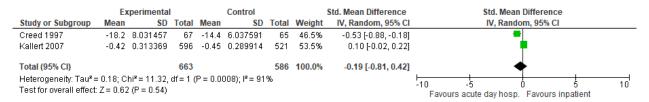


Figure 88: Remission (HAM-D<7/Present State Examination: Index of Definition ≤4)

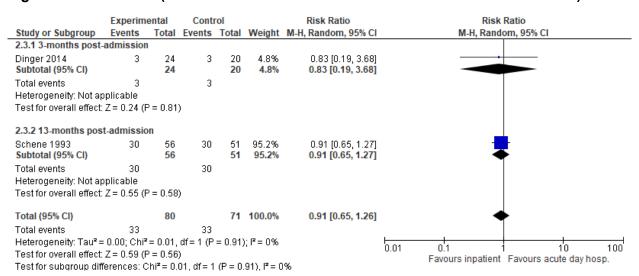
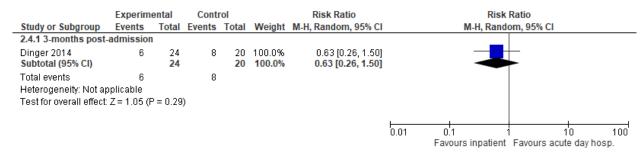


Figure 89: Response (at least 47% improvement on HAM-D)



### Important outcomes

Figure 90: Duration of index admission

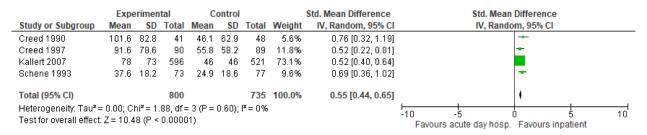


Figure 91: Readmission

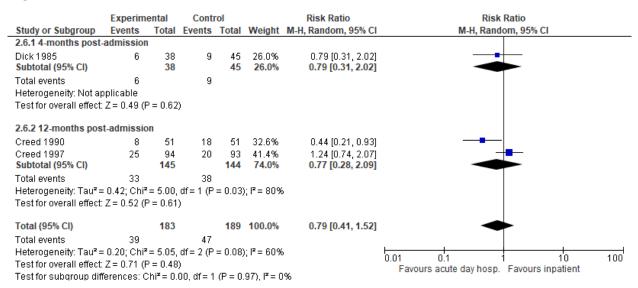


Figure 92: Service utilisation: Emergency contacts

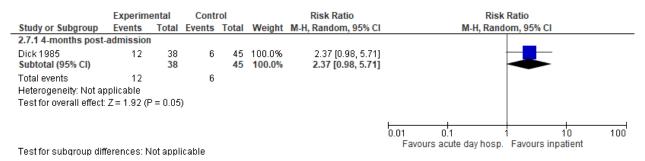
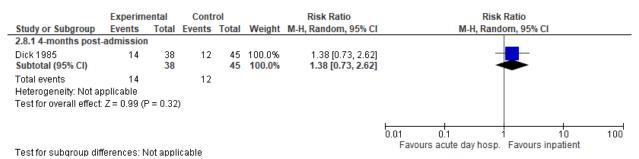


Figure 93: Service utilisation: Outpatient contact



### Figure 94: Quality of life (MANSA)

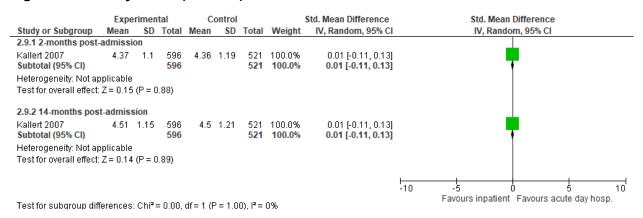


Figure 95: Social functioning impairment (GSDS-II)

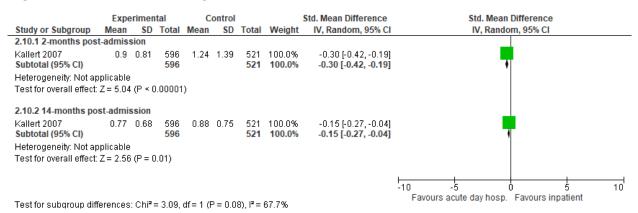


Figure 96: Social functioning response

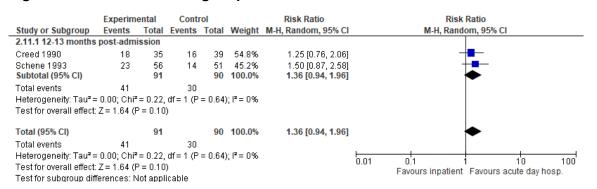
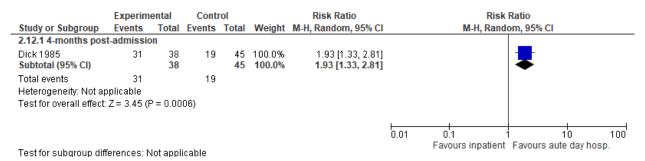


Figure 97: Satisfaction (number of participants satisfied or very satisfied with their treatment)



### Figure 98: Satisfaction (CAT)

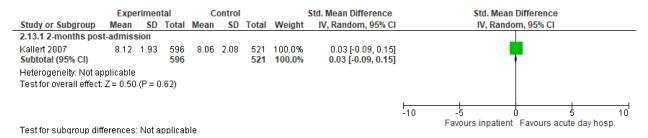
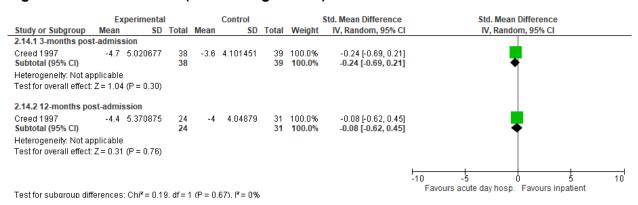
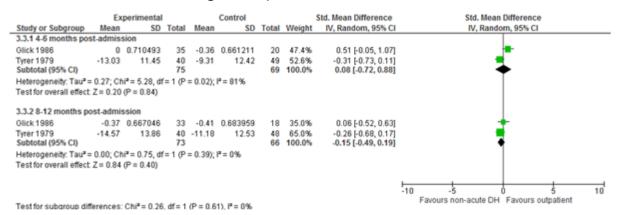


Figure 99: Carer distress (GHQ change score)



# Comparison 5. Non-acute day hospital care versus outpatient care (for adults with depression and non-psychotic severe mental illness)

Figure 100: Psychiatric symptom severity (Psychiatric Evaluation Form/Present State Examination; change score)



### Important outcomes

Figure 101: Service utilisation – admission as inpatient

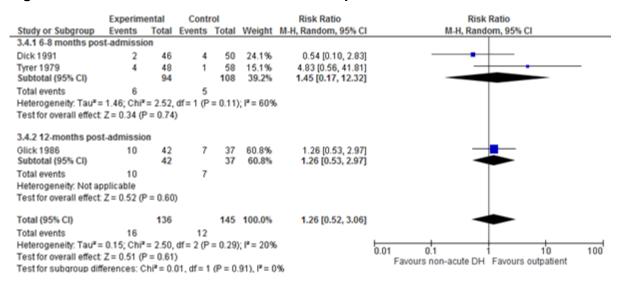
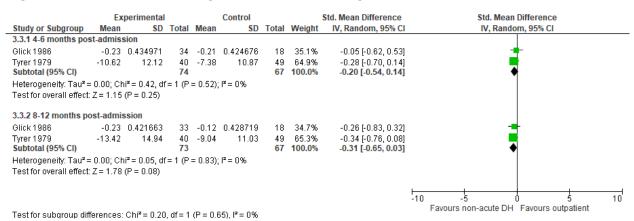


Figure 102: Social functioning (SAS-SR/SFS; change score)



## Figure 103: Global functioning (GAS; change score)

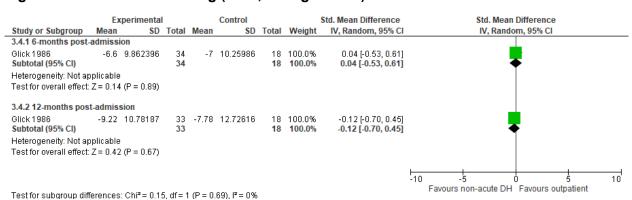
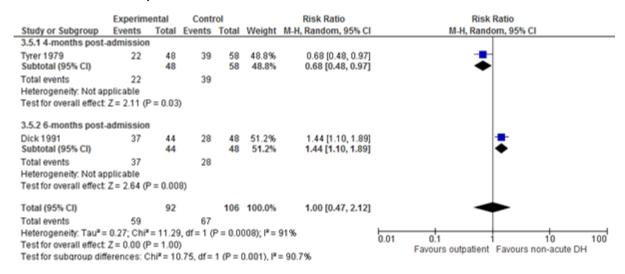


Figure 104: Satisfaction (number of participants satisfied or very satisfied with their treatment)



Comparison 6. Community mental health teams versus standard care (for adults with non-psychotic severe mental illness)

#### **Critical outcomes**

Figure 105: Psychiatric symptom severity (CPRS at endpoint)

|   | Experimental |        |          | Control |      |          | Std. Mean Difference |  | Std. Mean Difference                             |
|---|--------------|--------|----------|---------|------|----------|----------------------|--|--|
| Study or Subgroup   | Mean         | SD     | Total    | Mean    | SD   | Total    | Weight               | IV, Fixed, 95% CI                          | IV, Fixed, 95% CI                                |
| 5.3.1 3-months post   | entry-       |        |          |         |      |          |                      |  |  |
| Merson 1992<br>Subtotal (95% CI)  | 22.8         | 11     | 48<br>48 | 23.6    | 14.1 | 52<br>52 | 100.0%               | -0.06 [-0.45, 0.33]<br>-0.06 [-0.45, 0.33] |  |
| Heterogeneity: Not as<br>Test for overall effect                          |              | (P = 0 | 1.76)    |         |      |          |                      |  |  |
| Total (95% CI)  |              |        | 48       |         |      | 52       | 100.0%               | -0.06 [-0.45, 0.33]                        | <b>+</b>   |
| Heterogeneity: Not as<br>Test for overall effect<br>Test for subgroup dif | Z = 0.31     | 4      |          | nle     |      |          |                      |  | -10 -5 0 5 10 Favours CMHT Favours standard care |

# Important outcomes

Figure 106: Service utilisation – admission as inpatient

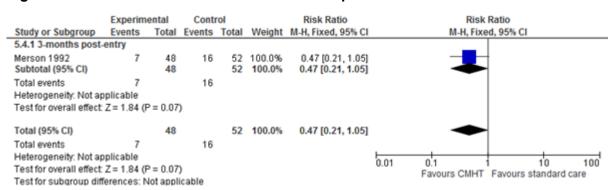


Figure 107: Service utilisation – admission as inpatient for >10 days

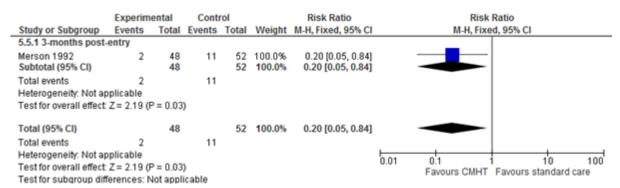


Figure 108: Satisfaction – number of participants satisfied with their treatment

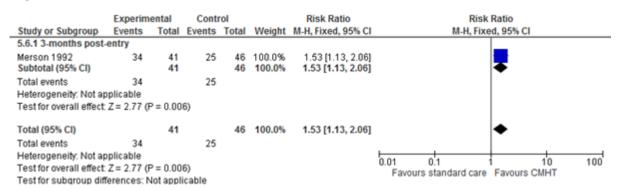


Figure 109: Satisfaction – service satisfaction score

