

## Additional file

**Table S1. 91 target genes by addictive drugs**

| Symbol         | Gene ID | Name   |
|----------------|---------|--|
| <i>ADH1A</i>   | 124     | alcohol dehydrogenase 1A (class I), alpha polypeptide                              |
| <i>ADH1B</i>   | 125     | alcohol dehydrogenase 1B (class I), beta polypeptide                               |
| <i>ADH1C</i>   | 126     | alcohol dehydrogenase 1C (class I), gamma polypeptide                              |
| <i>ADRA2A</i>  | 150     | adrenoceptor alpha 2A  |
| <i>ADRA2B</i>  | 151     | adrenoceptor alpha 2B  |
| <i>ADRA2C</i>  | 152     | adrenoceptor alpha 2C  |
| <i>AR</i>      | 367     | androgen receptor  |
| <i>ATP2C1</i>  | 27032   | ATPase, Ca <sup>++</sup> transporting, type 2C, member 1                           |
| <i>ATP5D</i>   | 513     | ATP synthase, H <sup>+</sup> transporting, mitochondrial F1 complex, delta subunit |
| <i>CALM1</i>   | 801     | calmodulin 1 (phosphorylase kinase, delta)   |
| <i>CALM2</i>   | 805     | calmodulin 2 (phosphorylase kinase, delta)   |
| <i>CALM3</i>   | 808     | calmodulin 3 (phosphorylase kinase, delta)   |
| <i>CARTPT</i>  | 9607    | CART prepropeptide   |
| <i>CHRM1</i>   | 1128    | cholinergic receptor, muscarinic 1   |
| <i>CHRM2</i>   | 1129    | cholinergic receptor, muscarinic 2   |
| <i>CHRNA10</i> | 57053   | cholinergic receptor, nicotinic, alpha 10 (neuronal)                               |
| <i>CHRNA2</i>  | 1135    | cholinergic receptor, nicotinic, alpha 2 (neuronal)                                |
| <i>CHRNA3</i>  | 1136    | cholinergic receptor, nicotinic, alpha 3 (neuronal)                                |
| <i>CHRNA4</i>  | 1137    | cholinergic receptor, nicotinic, alpha 4 (neuronal)                                |
| <i>CHRNA5</i>  | 1138    | cholinergic receptor, nicotinic, alpha 5 (neuronal)                                |
| <i>CHRNA6</i>  | 8973    | cholinergic receptor, nicotinic, alpha 6 (neuronal)                                |
| <i>CHRNA7</i>  | 1139    | cholinergic receptor, nicotinic, alpha 7 (neuronal)                                |
| <i>CHRNA9</i>  | 55584   | cholinergic receptor, nicotinic, alpha 9 (neuronal)                                |
| <i>CHRNB2</i>  | 1141    | cholinergic receptor, nicotinic, beta 2 (neuronal)                                 |
| <i>CHRNB3</i>  | 1142    | cholinergic receptor, nicotinic, beta 3 (neuronal)                                 |
| <i>CHRNB4</i>  | 1143    | cholinergic receptor, nicotinic, beta 4 (neuronal)                                 |
| <i>CNR1</i>    | 1268    | cannabinoid receptor 1 (brain)   |
| <i>CNR2</i>    | 1269    | cannabinoid receptor 2 (macrophage)  |
| <i>DRD2</i>    | 1813    | dopamine receptor D2   |
| <i>GABRA1</i>  | 2554    | gamma-aminobutyric acid (GABA) A receptor, alpha 1                                 |
| <i>GABRA2</i>  | 2555    | gamma-aminobutyric acid (GABA) A receptor, alpha 2                                 |
| <i>GABRA3</i>  | 2556    | gamma-aminobutyric acid (GABA) A receptor, alpha 3                                 |
| <i>GABRA4</i>  | 2557    | gamma-aminobutyric acid (GABA) A receptor, alpha 4                                 |
| <i>GABRA5</i>  | 2558    | gamma-aminobutyric acid (GABA) A receptor, alpha 5                                 |

|               |        |   |
|---------------|--------|---|
| <i>GABRA6</i> | 2559   | gamma-aminobutyric acid (GABA) A receptor, alpha 6  |
| <i>GABRB1</i> | 2560   | gamma-aminobutyric acid (GABA) A receptor, beta 1   |
| <i>GABRB2</i> | 2561   | gamma-aminobutyric acid (GABA) A receptor, beta 2   |
| <i>GABRB3</i> | 2562   | gamma-aminobutyric acid (GABA) A receptor, beta 3   |
| <i>GABRD</i>  | 2563   | gamma-aminobutyric acid (GABA) A receptor, delta  |
| <i>GABRE</i>  | 2564   | gamma-aminobutyric acid (GABA) A receptor, epsilon  |
| <i>GABRG1</i> | 2565   | gamma-aminobutyric acid (GABA) A receptor, gamma 1  |
| <i>GABRG2</i> | 2566   | gamma-aminobutyric acid (GABA) A receptor, gamma 2  |
| <i>GABRG3</i> | 2567   | gamma-aminobutyric acid (GABA) A receptor, gamma 3  |
| <i>GABRP</i>  | 2568   | gamma-aminobutyric acid (GABA) A receptor, pi   |
| <i>GABRQ</i>  | 55879  | gamma-aminobutyric acid (GABA) A receptor, theta  |
| <i>GABRR1</i> | 2569   | gamma-aminobutyric acid (GABA) A receptor, rho 1  |
| <i>GABRR2</i> | 2570   | gamma-aminobutyric acid (GABA) A receptor, rho 2  |
| <i>GABRR3</i> | 200959 | gamma-aminobutyric acid (GABA) A receptor, rho 3  |
| <i>GLRA1</i>  | 2741   | glycine receptor, alpha 1   |
| <i>GLRA2</i>  | 2742   | glycine receptor, alpha 2   |
| <i>GNG2</i>   | 54331  | guanine nucleotide binding protein (G protein), gamma 2   |
| <i>GRIA1</i>  | 2890   | glutamate receptor, ionotropic, AMPA 1  |
| <i>GRIA2</i>  | 2891   | glutamate receptor, ionotropic, AMPA 2  |
| <i>GRIK2</i>  | 2898   | glutamate receptor, ionotropic, kainate 2   |
| <i>GRIN1</i>  | 2902   | glutamate receptor, ionotropic, N-methyl D-aspartate 1  |
| <i>GRIN2A</i> | 2903   | glutamate receptor, ionotropic, N-methyl D-aspartate 2A   |
| <i>GRIN2B</i> | 2904   | glutamate receptor, ionotropic, N-methyl D-aspartate 2B   |
| <i>GRIN2C</i> | 2905   | glutamate receptor, ionotropic, N-methyl D-aspartate 2C   |
| <i>GRIN2D</i> | 2906   | glutamate receptor, ionotropic, N-methyl D-aspartate 2D   |
| <i>GRIN3A</i> | 116443 | glutamate receptor, ionotropic, N-methyl-D-aspartate 3A   |
| <i>GRIN3B</i> | 116444 | glutamate receptor, ionotropic, N-methyl-D-aspartate 3B   |
| <i>HTR2A</i>  | 3356   | 5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled                                      |
| <i>KCNA1</i>  | 3736   | potassium voltage-gated channel, shaker-related subfamily, member 1 (episodic ataxia with myokymia) |
| <i>KCNJ3</i>  | 3760   | potassium inwardly-rectifying channel, subfamily J, member 3  |
| <i>KCNJ6</i>  | 3763   | potassium inwardly-rectifying channel, subfamily J, member 6  |
| <i>KCNK3</i>  | 3777   | potassium channel, subfamily K, member 3  |
| <i>KCNK9</i>  | 51305  | potassium channel, subfamily K, member 9  |
| <i>KCNMA1</i> | 3778   | potassium large conductance calcium-activated channel, subfamily M, alpha member 1                  |
| <i>KCNN4</i>  | 3783   | potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4           |
| <i>MAOA</i>   | 4128   | monoamine oxidase A   |
| <i>MAOB</i>   | 4129   | monoamine oxidase B   |
| <i>MT-ND1</i> | 4535   | NADH dehydrogenase, subunit 1 (complex I)   |
| <i>NPSR1</i>  | 387129 | neuropeptide S receptor 1   |
| <i>OPRD1</i>  | 4985   | opioid receptor, delta 1  |

|                |        |   |
|----------------|--------|---|
| <i>OPRK1</i>   | 4986   | opioid receptor, kappa 1  |
| <i>OPRM1</i>   | 4988   | opioid receptor, mu 1   |
| <i>PTGS1</i>   | 5742   | prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase) |
| <i>PTGS2</i>   | 5743   | prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase) |
| <i>RHO</i>     | 6010   | rhodopsin   |
| <i>SCN10A</i>  | 6336   | sodium channel, voltage-gated, type X, alpha subunit                                  |
| <i>SCN11A</i>  | 11280  | sodium channel, voltage-gated, type XI, alpha subunit                                 |
| <i>SCN5A</i>   | 6331   | sodium channel, voltage-gated, type V, alpha subunit                                  |
| <i>SIGMAR1</i> | 10280  | sigma non-opioid intracellular receptor 1   |
| <i>SLC18A1</i> | 6570   | solute carrier family 18 (vesicular monoamine), member 1                              |
| <i>SLC18A2</i> | 6571   | solute carrier family 18 (vesicular monoamine), member 2                              |
| <i>SLC6A2</i>  | 6530   | solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2        |
| <i>SLC6A3</i>  | 6531   | solute carrier family 6 (neurotransmitter transporter, dopamine), member 3            |
| <i>SLC6A4</i>  | 6532   | solute carrier family 6 (neurotransmitter transporter, serotonin), member 4           |
| <i>TAAR1</i>   | 134864 | trace amine associated receptor 1   |
| <i>TACR1</i>   | 6869   | tachykinin receptor 1   |
| <i>TSPO</i>    | 706    | translocator protein (18kDa)  |

**Table S2. The network properties and literature search results of non-addictive drugs**

| Drug name                          | Expanded addictive network |             | Literature search evaluation     |                                  |                                |
|------------------------------------|----------------------------|-------------|----------------------------------|----------------------------------|--------------------------------|
|                                    | Degree                     | Betweenness | Number of abstracts <sup>a</sup> | Number of abstracts <sup>b</sup> | Fisher's exact <i>P</i> -value |
| 3,4-Methylenedioxy methamphetamine | 5                          | 0.0041      | 590                              | 1834                             | 0                              |
| Aripiprazole                       | 7                          | 0.0045      | 91                               | 2225                             | 0                              |
| Bromazepam                         | 19                         | 0.0025      | 43                               | 500                              | 0                              |
| Desipramine                        | 5                          | 0.0032      | 188                              | 7412                             | 0                              |
| Dextroamphetamine                  | 4                          | 0.0018      | 417                              | 6578                             | 0                              |
| Dronabinol                         | 2                          | 0.1667      | 30                               | 189                              | 0                              |
| Ephedra                            | 10                         | 0.0280      | 36                               | 683                              | 0                              |
| Ergotamine                         | 5                          | 0.0025      | 101                              | 2807                             | 0                              |
| Ethchlorvynol                      | 9                          | 0.0012      | 23                               | 246                              | 0                              |
| Flurazepam                         | 19                         | 0.0025      | 37                               | 1131                             | 0                              |
| Meprobamate                        | 6                          | 0.0003      | 121                              | 2466                             | 0                              |
| Nitrazepam                         | 19                         | 0.0025      | 50                               | 1201                             | 0                              |
| Nortriptyline                      | 5                          | 0.0032      | 64                               | 2720                             | 0                              |
| Olanzapine                         | 7                          | 0.0045      | 185                              | 6493                             | 0                              |
| Oxazepam                           | 19                         | 0.0025      | 119                              | 1723                             | 0                              |
| Paroxetine                         | 5                          | 0.0032      | 134                              | 5056                             | 0                              |

|                      |    |        |      |       |                        |
|----------------------|----|--------|------|-------|------------------------|
| Phentermine          | 5  | 0.0103 | 58   | 844   | 0                      |
| Pramipexole          | 5  | 0.0007 | 33   | 1004  | 0                      |
| Pseudoephedrine      | 4  | 0.0014 | 82   | 1152  | 0                      |
| Risperidone          | 5  | 0.0007 | 170  | 7288  | 0                      |
| Temazepam            | 20 | 0.0030 | 100  | 964   | 0                      |
| Varenicline          | 4  | 0.0017 | 191  | 887   | 0                      |
| Zopiclone            | 5  | 0.0006 | 87   | 847   | 0                      |
| Butalbital           | 10 | 0.0037 | 17   | 126   | $8.70 \times 10^{-14}$ |
| 4-Methoxyamphetamine | 6  | 0.0151 | 15   | 86    | $3.82 \times 10^{-13}$ |
| Clorazepate          | 20 | 0.0030 | 21   | 441   | $2.45 \times 10^{-12}$ |
| Tramadol             | 6  | 0.0463 | 210  | 3020  | $2.51 \times 10^{-11}$ |
| Amitriptyline        | 9  | 0.0517 | 103  | 7922  | $4.23 \times 10^{-11}$ |
| Methadone            | 4  | 0.0192 | 5328 | 12684 | $1.40 \times 10^{-10}$ |
| Quetiapine           | 7  | 0.0045 | 129  | 3229  | $2.38 \times 10^{-10}$ |
| Clozapine            | 7  | 0.0045 | 235  | 9594  | $2.68 \times 10^{-10}$ |
| Clonazepam           | 19 | 0.0029 | 103  | 3658  | $2.98 \times 10^{-10}$ |
| Flumazenil           | 4  | 0.0002 | 89   | 4005  | $3.58 \times 10^{-10}$ |
| Apomorphine          | 5  | 0.0007 | 153  | 11082 | $3.98 \times 10^{-10}$ |
| Doxepin              | 9  | 0.0101 | 30   | 1238  | $1.04 \times 10^{-9}$  |
| Midazolam            | 19 | 0.0025 | 119  | 10570 | $5.19 \times 10^{-9}$  |
| Tenocyclidine        | 6  | 0.0019 | 13   | 270   | $2.77 \times 10^{-8}$  |
| Eszopiclone          | 5  | 0.0006 | 10   | 174   | $2.14 \times 10^{-7}$  |
| Escitalopram         | 4  | 0.0020 | 25   | 1203  | $4.25 \times 10^{-7}$  |
| Imipramine           | 5  | 0.0032 | 124  | 12204 | $5.16 \times 10^{-7}$  |
| Nefazodone           | 5  | 0.0026 | 18   | 691   | $7.55 \times 10^{-7}$  |
| Ziprasidone          | 7  | 0.0045 | 27   | 1516  | $2.74 \times 10^{-6}$  |
| Bromocriptine        | 5  | 0.0007 | 88   | 8422  | $7.46 \times 10^{-6}$  |
| Yohimbine            | 5  | 0.0007 | 88   | 8603  | $1.60 \times 10^{-5}$  |
| Lisuride             | 5  | 0.0007 | 19   | 952   | $1.68 \times 10^{-5}$  |
| Barbital             | 10 | 0.0037 | 28   | 1827  | $2.72 \times 10^{-5}$  |
| Mianserin            | 4  | 0.0015 | 39   | 3038  | $4.48 \times 10^{-5}$  |
| Estazolam            | 16 | 0.0020 | 7    | 156   | $6.91 \times 10^{-5}$  |
| Pergolide            | 5  | 0.0007 | 18   | 1103  | $3.28 \times 10^{-4}$  |
| Prazepam             | 16 | 0.0020 | 7    | 208   | $4.04 \times 10^{-4}$  |
| Butabarbital         | 10 | 0.0037 | 4    | 55    | $4.21 \times 10^{-4}$  |
| Methotrimeprazine    | 7  | 0.0045 | 13   | 722   | $8.72 \times 10^{-4}$  |
| Ropinirole           | 5  | 0.0007 | 12   | 652   | $1.13 \times 10^{-3}$  |
| Halazepam            | 16 | 0.0020 | 3    | 57    | $5.73 \times 10^{-3}$  |
| Fludiazepam          | 16 | 0.0020 | 2    | 27    | 0.01                   |
| Paliperidone         | 5  | 0.0007 | 6    | 375   | 0.03                   |
| Orphenadrine         | 6  | 0.0221 | 8    | 588   | 0.04                   |
| Promethazine         | 4  | 0.0018 | 30   | 3516  | 0.07                   |
| Promazine            | 4  | 0.0018 | 13   | 1284  | 0.07                   |

|                              |    |        |     |       |      |
|------------------------------|----|--------|-----|-------|------|
| Propiomazine                 | 4  | 0.0018 | 2   | 68    | 0.07 |
| Amoxapine                    | 6  | 0.1018 | 5   | 426   | 0.14 |
| Adinazolam                   | 16 | 0.0020 | 2   | 108   | 0.15 |
| Trimipramine                 | 6  | 0.0048 | 5   | 469   | 0.18 |
| Ketazolam                    | 6  | 0.0009 | 1   | 34    | 0.19 |
| Clobazam                     | 19 | 0.0025 | 6   | 655   | 0.24 |
| Galantamine                  | 11 | 0.0148 | 12  | 1553  | 0.28 |
| Clotiazepam                  | 16 | 0.0020 | 1   | 55    | 0.29 |
| Chloroprocaine               | 4  | 0.0124 | 3   | 417   | 0.49 |
| Cabergoline                  | 5  | 0.0007 | 7   | 1124  | 0.56 |
| Quazepam                     | 15 | 0.0018 | 1   | 143   | 0.60 |
| Chlorprothixene              | 4  | 0.0018 | 3   | 660   | 0.79 |
| Zonisamide                   | 4  | 0.0135 | 4   | 961   | 0.86 |
| Primidone                    | 10 | 0.0037 | 7   | 1648  | 0.90 |
| Flufenamic Acid              | 3  | 0.1088 | 2   | 1267  | 1.00 |
| Procaine                     | 4  | 0.0186 | 53  | 12524 | 1.00 |
| Hexobarbital                 | 10 | 0.0037 | 6   | 2706  | 1.00 |
| Thiopental                   | 10 | 0.0037 | 27  | 8039  | 1.00 |
| Alpha-D-Mannose              | 2  | 0.1403 | 0   | 279   | 1.00 |
| Aprobarbital                 | 10 | 0.0037 | 0   | 19    | 1.00 |
| Barbituric acid derivative   | 10 | 0.0037 | 0   | 23    | 1.00 |
| Beta-D-Mannose               | 2  | 0.1403 | 0   | 39    | 1.00 |
| Butethal                     | 10 | 0.0037 | 0   | 4     | 1.00 |
| Cinolazepam                  | 16 | 0.0020 | 0   | 5     | 1.00 |
| Ginkgobiloba                 | 5  | 0.0268 | 0   | 3     | 1.00 |
| Glycine                      | 5  | 0.0010 | 216 | 62562 | 1.00 |
| Heptabarbital                | 10 | 0.0037 | 0   | 31    | 1.00 |
| Lauryl Dimethylamine-N-Oxide | 2  | 0.0692 | 0   | 7     | 1.00 |
| L-Glutamic Acid              | 10 | 0.0199 | 0   | 2301  | 1.00 |
| Metharbital                  | 10 | 0.0037 | 0   | 19    | 1.00 |
| Methylphenobarbital          | 10 | 0.0037 | 0   | 47    | 1.00 |
| Minaprine                    | 5  | 0.0088 | 0   | 112   | 1.00 |
| NADH                         | 4  | 0.0051 | 36  | 29140 | 1.00 |
| Talbutal                     | 10 | 0.0037 | 0   | 3     | 1.00 |
| Quinidine barbiturate        | 4  | 0.0322 | 1   | 0     | 1.00 |

<sup>a</sup>The number of abstracts based on having both the drug name and at least one addiction-related keyword in an abstract.

<sup>b</sup>The number of abstracts is based on the drug name in an abstract.