Aminorex, Fenfluramine, and Chlorphentermine Are Serotonin Transporter Substrates
Implications for Primary Pulmonary Hypertension

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Background—Coadministration of phentermine and fenfluramine (phen/fen) effectively treats obesity and possibly addictive disorders. The association of fenfluramine and certain other anorexic agents with serious side effects, such as cardiac valvulopathy and primary pulmonary hypertension (PPH), limits the clinical utility of these drugs. Development of new medications that produce neurochemical effects like phen/fen without causing unwanted side effects would be a significant therapeutic breakthrough.

Methods and Results—We tested the hypothesis that fenfluramine (and other anorexic agents) might increase the risk of PPH through interactions with serotonin (5-HT) transporters. Because 5-HT transporter proteins in the lung and brain are identical, we examined, in rat brain, the effects of selected drugs on 5-HT efflux in vivo and monoamine transporters in vitro as a generalized index of transporter function. Our data show that drugs known or suspected to increase the risk of PPH (eg, aminorex, fenfluramine, and chlorphentermine) are 5-HT transporter substrates, whereas drugs that have not been shown to increase the risk of PPH are less potent in this regard.

Conclusions—We speculate that medications that are 5-HT transporter substrates get translocated into pulmonary cells where, depending on the degree of drug retention, their intrinsic drug toxicity, and individual susceptibility, PPH could develop as a response to high levels of these drugs or metabolites. Emerging evidence suggests that it is possible to develop transporter substrates devoid of adverse side effects. Such medications could have therapeutic application in the management of obesity, drug dependence, depression, and other disorders. (Circulation. 1999;100:869-875.)

Key Words: pulmonary heart disease • hypertension • drugs • obesity
isolated rat lung. Accordingly, this group proposed that inhibition of pulmonary K⁺ channels could lead to PPH in susceptible individuals by increasing pulmonary blood pressure and stimulating fibroblast growth.

In the current study, we investigated the hypothesis that 5-HT transporters (SERTs) might be a critical locus of action for drugs linked to PPH. Lung tissue contains SERTs identical to that of brain,¹⁶ which serve to accumulate circulating 5-HT and serotonergic drugs (ie, antidepressants) into pulmonary cells.¹⁶ To this end, fenfluramine releases endogenous 5-HT from neurons by an exchange-diffusion process mediated by SERT sites in the brain:¹⁷ The transport of fenfluramine into the nerve terminal by the SERT causes the reverse transport of 5-HT out of the nerve terminal. However, much less is known about the role of SERTs in the biological effects of aminorex, chlorphentermine, and other appetite suppressants. We therefore evaluated the effects of aminorex, fenfluramine, d-fenfluramine, and chlorphentermine on 5-HT efflux in rat brain as a generalized in vivo index of SERT function. We also examined the activity of these same drugs in assays of SERT binding and [³H]-5-HT uptake in vitro for comparative purposes. Our findings show that all of the drugs known to increase the risk of PPH are potent SERT substrates. Accordingly, the pulmonary SERT may function as a "gateway" facilitating the accumulation and subsequent toxicity of such drugs, which ultimately leads to PPH.

Methods

Animals
Male Sprague-Dawley rats (Charles River, Wilmington, Mass) weighing 280 to 320 g were housed in standard vivarium conditions (lights on from 7 AM to 7 PM) with food and water freely available. Animals were maintained in facilities fully accredited by the American Association of the Accreditation of Laboratory Animal Care, and experiments were performed in accordance with the Institutional Care and Use Committee of the National Institute on Drug Abuse (NIDA), Division of Intramural Research.

Drugs and Reagents
d,l-Fenfluramine HCl (fenfluramine, FW 267.7), d-fenfluramine HCl (FW 267.7), chlorphentermine HCl (FW 220.2), d-amphetamine sulfate (FW 368.5), phentermine HCl (FW 185.7), and pentobarbital sodium were obtained from the Addiction Research Center Pharmacy (NIDA, National Institutes of Health, Baltimore, Md). Metohxylfluamine (Metofane) was purchased from Pittman-Moore. Aminorex (FW 162.2) was purchased from Research Biochemicals Inc. The sources of other reagents are published.¹⁸⁻²⁰

In Vivo Microdialysis Procedures
Surgical and microdialysis procedures were carried out with modifications of previously described methods.¹⁸ On the morning after implantation of microdialysis probes (2×0.5 mm exchange surface, CMA/12, CMA/Microdialysis) in the nucleus accumbens, dialysate samples were collected at 20-minute intervals. Samples were immediately assayed for DA and 5-HT as described elsewhere.¹⁸ Three baseline samples were collected and all subsequent monoamine measures were expressed as a percentage of this baseline. Data were evaluated by 1-way (drug treatment) ANOVA. When significant F values were obtained, Newman-Keuls post hoc tests were performed to compare group means. A value of P<0.05 was chosen as the minimum criterion for statistical significance. For binding and uptake inhibition studies, the data of 3 experiments were pooled and fit to the 2-parameter logistic equation for the best-fit estimates of the IC₅₀ and slope factor by use of MLAB-PC (Civilized Software) as described elsewhere.²⁰ The Kᵢ values were then determined with the use of the equation IC₅₀/ [1+(L/Kᵢ)], where L is the concentration of the agonist and Kᵢ is its dissociation constant.

Results

In Vivo Microdialysis Experiments
Figure 1 shows the chemical structures of the amphetamine analogues tested in this study. The effects of aminorex, fenfluramine, d-fenfluramine, and chlorphentermine on
dialysate DA and 5-HT in rat nucleus accumbens are depicted in Figure 2. Mean preinjection baseline dialysate levels of DA and 5-HT collected from all rats used in these experiments (n=20) were 1.96±0.34 nmol/L and 0.53±0.11 nmol/L, respectively. Aminorex significantly increased dialysate levels of DA \[ F(8,36)=41.50, \ P<0.0001 \] and 5-HT \[ F(8,36)=101.18, \ P<0.0001 \]; post hoc tests revealed that both doses of aminorex significantly increased DA and 5-HT. The stimulatory effect of aminorex on DA and 5-HT efflux was similar in magnitude after 3 \( \times \) mol/kg (ie, ’3-fold), whereas the effect of the drug on 5-HT was more pronounced after 10 \( \times \) mol/kg (ie, 10-fold for 5-HT compared with 6-fold for DA). Fenfluramine significantly increased dialysate 5-HT \[ F(8,36)=26.80, \ P<0.0001 \] without affecting levels of DA \[ F(8,36)=1.21, \ P<0.32 \]; post hoc tests showed that both doses of fenfluramine significantly increased 5-HT efflux. \( d \)-Fenfluramine elevated dialysate 5-HT \[ F(8,36)=12.61, \ P<0.0001 \] but not DA \[ F(8,36)=0.64, \ P<0.74 \]. Chlorphentermine elevated 5-HT \[ F(8,36)=29.06, \ P<0.0001 \] and DA \[ F(8,36)=7.17, \ P<0.01 \], with a greater effect on 5-HT. For example, 3 \( \mu \)mol/kg chlorphentermine selectively increased 5-HT 4-fold, whereas 10 \( \mu \)mol/kg increased 5-HT 7-fold and DA 2-fold. Aminorex profoundly increased motor activity and stereotypic patterned sniffing (nonquantified observation), whereas the other 3 agents had minimal effects on these parameters. These observations agree with the reported psychomotor stimulant actions of aminorex compared with the lack of such actions with fenfluramine.21-22

In Vitro Characterization of Test Drugs
The activity of test drugs was assessed in 2 assays: (1) uptake inhibition assays, which detect not only transport uptake inhibitors but also transporter-mediated releasers (ie, substrates), and (2) transporter binding assays, which measure the affinity of drugs for a high-affinity recognition site on the DA transporter (DAT) and SERT, which mediates inhibition of transmitter uptake. Accumulating evidence indicates that reuptake inhibitors (ie, cocaine) and releasers (ie, substrates) interact with transporter proteins in a distinctive manner and can be discriminated from each other under a variety of assay conditions.23-26 A number of reference compounds were included in these experiments for comparative purposes.

The results obtained for the DA system are presented in Table 1. Established DA uptake inhibitors had similar potency in uptake and binding assays, yielding low binding-to-uptake ratios (ie, <2). For example, the cocaine analogue \( 2\beta\)-carbomethoxy-\( 3\beta\)-(4-fluorophenyl)tropane (CFT) had an \( K_i \) value of 35 nmol/L in the \([3H]DA \) assay and a \( K_i \) value of 45 nmol/L in the \([125I]\)RTI-55 binding assay. In contrast, established DAT substrates such as \( d \)-amphetamine and DA23,24 were much more potent as inhibitors of \([3H]DA \) uptake than of \([125I]\)RTI-55-labeled DAT binding, yielding high binding-to-uptake ratios (ie, >10). For example, \( d \)-amphetamine had a \( K_i \) value of 34 nmol/L in the \([3H]DA \) uptake assay, a \( K_i \) value of 19800 nmol/L in the \([125I]\)RTI-55 binding assay and a binding-to-uptake ratio of 582. Thus the method of calculating binding-to-uptake ratios described herein can be used to distinguish DA uptake inhibitors from DAT substrates. Phentermine was nearly 50-fold less potent in the uptake assay when compared with \( d \)-amphetamine, and the drug exhibited a binding-to-uptake ratio of 50, indicative of a substrate. Aminorex was more potent than phentermine in the \([3H]DA \) uptake assay (\( K_i =216 \) nmol/L) but had a binding-to-uptake ratio consistent with a DA uptake inhibitor, not a substrate. Chlorphentermine was approximately as potent as phentermine in the \([3H]DA \) uptake assay and...
potent in the [3H]5-HT uptake assay (K_i = 1244 nmol/L) and had a binding-to-uptake ratio of 22, consistent with being a substrate for SERT. 5-HT, fenfluramine, and d-fenfluramine, which are established substrates of SERT, were potent in the [3H]5-HT uptake assay and had high binding-to-uptake ratios of 52, 174, and 393, respectively. Chlorphentermine, like fenfluramine, was a potent inhibitor of [3H]5-HT uptake and exhibited a high binding-to-uptake ratio indicative of a substrate.

**Discussion**

A primary objective of the current study was to assess the possible role of SERT sites in mediating the effects of drugs that increase the risk of PPH. As summarized in Table 3, aminorex, fenfluramine, d-fenfluramine, and chlorphentermine all share the ability to increase extracellular levels of 5-HT in rat brain when administered at doses known to decrease feeding.21 The in vitro findings further suggest that these drugs are SERT substrates, causing 5-HT efflux by a process involving exchange of drug molecules for endogenous 5-HT. Recent studies show that the level of expression of SERT in human lung was much greater than in human brain, indicating that SERTs in the lung probably represent a major site of action for aminorex, fenfluramine, and chlorphentermine.

The microdialysis data indicate that drugs that increase the risk of PPH increase extracellular 5-HT, yet the effects of the drugs on extracellular DA differed considerably. Collectively, the in vivo microdialysis results demonstrate that appetite suppressants with similar anorexic potency exhibit very different effects on DA systems in the brain.

The microdialysis data alone cannot explain the precise mechanism(s) responsible for drug-induced increases in transmitter efflux. We used in vitro assay methods to determine the specific mechanism(s) of action of selected anorexic agents. The assays used in the present work evaluated different aspects of drug interactions with DAT and SERT. The [125I]RTI-55 binding assay measures the affinity of test drugs for a high-affinity recognition site on the transporter, which mediates inhibition of neurotransmitter uptake.20 As such, the potency of an uptake blocker in assays of ligand binding is highly correlated with its potency in assays of uptake inhibition.27,28 Because substrates inhibit uptake through 2 mechanisms, substrates are more potent at inhibiting uptake than binding.29 This is consistent with emerging evidence that uptake inhibitors and substrates bind to different domains on transporter proteins30,31 and that the activity of drugs at these discrete sites can be discriminated under a variety of experimental conditions.23,25

On the basis of the above considerations, we hypothesized that the ratio of transporter binding to transmitter reuptake (binding-to-uptake ratio) for a particular drug could be used to differentiate reuptake blockers from substrate-type releasers. Although thermodynamic effects related to assay conditions may play a role in the exact value of the ratio, in general, reuptake blockers would be predicted to have binding-to-reuptake ratios close to unity, whereas substrate-type releasers would have ratios much greater than unity. The present in vitro data support this proposal. At DAT sites (see Table 1),

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**TABLE 1. Interaction of Test Agents With DAT**

<table>
<thead>
<tr>
<th>Drug</th>
<th>[3H]DA Uptake K_i, nmol/L</th>
<th>[125I]RTI-55 Binding K_i, nmol/L</th>
<th>Binding/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established DAT substrates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenetermine</td>
<td>1580±80</td>
<td>79 800±3200</td>
<td>50.5</td>
</tr>
<tr>
<td>(+) Amphetamine</td>
<td>34±6</td>
<td>19 800±870</td>
<td>582</td>
</tr>
<tr>
<td>Dopamine</td>
<td>38.3±1.6*</td>
<td>62 100±2220</td>
<td>1621</td>
</tr>
</tbody>
</table>

**Established DAT inhibitors**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>CFT†</td>
<td>35.0±2.9</td>
<td>45.0±2.3</td>
<td>1.3</td>
</tr>
<tr>
<td>GBR12935†</td>
<td>4.90±0.30</td>
<td>0.79±0.08</td>
<td>0.16</td>
</tr>
<tr>
<td>RTI-55†</td>
<td>0.83±0.09</td>
<td>0.76±0.08</td>
<td>0.91</td>
</tr>
</tbody>
</table>

**Test agents**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>d-Fenfluramine</td>
<td>22 000±1100</td>
<td>70 000±2300</td>
<td>3.2</td>
</tr>
<tr>
<td>Aminorex</td>
<td>216±7</td>
<td>784±16</td>
<td>3.6</td>
</tr>
<tr>
<td>Chlorphentermine</td>
<td>3940±110</td>
<td>11 900±125</td>
<td>3.0</td>
</tr>
<tr>
<td>(±) Fenfluramine</td>
<td>23 700±1300</td>
<td>113 000±6600</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*Data from Reference 19.
†Data from Reference 42.

K_i values of selected agents at the DAT measured with [125I]RTI-55 in rat caudate membranes and K_i values for inhibition of [3H]DA uptake are reported above (mean±SD, n=3).

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**TABLE 2. Interaction of Test Agents With 5-HT Transporter**

<table>
<thead>
<tr>
<th>Drug</th>
<th>[3H]5-HT Uptake K_i, nmol/L</th>
<th>[125I]RTI-55 Binding K_i, nmol/L</th>
<th>Binding/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established SERT substrates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT</td>
<td>17.4±0.8*</td>
<td>6850±170</td>
<td>393</td>
</tr>
<tr>
<td>Dextfenfluramine</td>
<td>234±7</td>
<td>12 160±780</td>
<td>52.0</td>
</tr>
<tr>
<td>(±) Fenfluramine</td>
<td>148±5</td>
<td>25 800±2000</td>
<td>174</td>
</tr>
</tbody>
</table>

**Established SERT inhibitors**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine†</td>
<td>0.61±0.04</td>
<td>0.033±0.008</td>
<td>0.05</td>
</tr>
<tr>
<td>Clomipramine†</td>
<td>0.30±0.01</td>
<td>1.10±0.06</td>
<td>3.7</td>
</tr>
<tr>
<td>Cocaine†</td>
<td>190±7</td>
<td>129±9</td>
<td>0.70</td>
</tr>
<tr>
<td>Fluoxetine†</td>
<td>8.0±0.6</td>
<td>17.7±1.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

**Test agents**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminorex</td>
<td>1244±106</td>
<td>27 700±990</td>
<td>22.3</td>
</tr>
<tr>
<td>Chlorphentermine</td>
<td>338±6</td>
<td>23 000±1050</td>
<td>68.0</td>
</tr>
<tr>
<td>Phenetermine</td>
<td>13 900±510</td>
<td>91 340±4800</td>
<td>6.6</td>
</tr>
<tr>
<td>(±) Aminorex</td>
<td>3830±170</td>
<td>46 800±2400</td>
<td>12.2</td>
</tr>
</tbody>
</table>

*Data from Reference 19.
†Uptake data from Reference 20 and binding data from Reference 20.

K_i values of selected agents at the 5-HT transporter measured with [125I]RTI-55 in rat caudate membranes and K_i values for inhibition of [3H]5-HT uptake are reported above (mean±SD, n=3).
TABLE 3. Summary of Results

<table>
<thead>
<tr>
<th>Anorexic Drug</th>
<th>Activity at DAT</th>
<th>Activity at SERT</th>
<th>Effect on DA Efflux</th>
<th>Effect on 5-HT Efflux</th>
<th>Linked to PPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-Amphetamine</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Increase</td>
<td>Weak effect</td>
<td>No</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Substrate</td>
<td>Weak substrate/uptake inhibitor</td>
<td>Increase</td>
<td>Weak effect</td>
<td>Yes</td>
</tr>
<tr>
<td>Aminorex</td>
<td>Uptake inhibitor</td>
<td>Substrate</td>
<td>Increase</td>
<td>Increase</td>
<td>Yes</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>Inactive</td>
<td>Substrate</td>
<td>No effect</td>
<td>Increase</td>
<td>Yes</td>
</tr>
<tr>
<td>d-Fenfluramine</td>
<td>Inactive</td>
<td>Substrate</td>
<td>No effect</td>
<td>Increase</td>
<td>Yes</td>
</tr>
<tr>
<td>Chlorphentermine</td>
<td>Uptake inhibitor</td>
<td>Substrate</td>
<td>Weak effect</td>
<td>Increase</td>
<td>Possibly</td>
</tr>
</tbody>
</table>

Summary of the relation between transporter activity, monoamine efflux, and risk of PPH for anorexic medications. The classification of a drug as a substrate or uptake inhibitor is based on the binding-to-uptake ratio for that drug; ratios ≥ 10 are considered to be indicative of substrate activity.

drugs known to be substrates (ie, amphetamine\textsuperscript{23,24} and DA) had binding-to-uptake ratios > 10, whereas agents known to be uptake inhibitors had binding-to-uptake ratios < 2. Thus only DA, amphetamine, and phentermine were clearly DAT substrates in our assays. At SERT sites (see Table 2), drugs known to be substrates (ie, 5-HT and fenfluramine) had binding-to-uptake ratios > 10, whereas agents known to be uptake inhibitors had binding-to-uptake ratios < 4. In this case aminorex, fenfluramine, d-fenfluramine, and chlorphentermine were clearly SERT substrates with potencies ≤ 1 μmol/L. Amphetamine, which other work demonstrates is a SERT substrate,\textsuperscript{33} was tested in our system as a weak SERT substrate. The results with phentermine were indeterminate, with it being either a low-potency SERT uptake inhibitor or substrate. It is noteworthy that our classification of anorexic agents as either reuptake blockers or substrate-type releasers (summarized in Table 3) is in excellent agreement with data obtained by use of various sophisticated in vitro techniques.\textsuperscript{23,25}

The anorexic medications examined here are often grouped together on the basis of similarities in chemical structure (ie, \(\beta\)-phenethylamines) and therapeutic indication (ie, appetite suppression). Because our data show that these drugs have widely different profiles of activity at DAT and SERT sites in the brain, it is not unreasonable that these drugs might also be associated with very different side effects. Whereas rigorous epidemiological investigations have demonstrated that aminorex, fenfluramine, and d-fenfluramine increase the risk of PPH,\textsuperscript{3,6} such data are lacking for other anorexic medications, for which there exist only a few isolated case reports of medication-associated PPH.\textsuperscript{7,8} Case reports do not provide a scientific basis for concluding that a drug increases the risk of developing PPH. Unfortunately, many authors have generalized the potential dangers of PPH to all “amphetamines,” “anorexic agents,” “anorexigens,” and “appetite suppressants.”\textsuperscript{3,5,33}

As summarized in Table 3, our data indicate that anorexic agents that increase the risk of developing PPH are SERT substrates and increase extracellular 5-HT at therapeutically relevant doses. So the fundamental question remains: How might SERT substrate activity be involved in causing PPH? As alluded to previously, some investigators have hypothesized that drug-induced elevations in circulating 5-HT, secondary to 5-HT release from platelets, might be involved in drug-induced PPH.\textsuperscript{10} However, this proposal is not consistent with the finding that fenfluramine actually lowers blood 5-HT and does not increase plasma 5-HT.\textsuperscript{11–13} This effect of fenfluramine follows directly from its mechanism of action: blockade of 5-HT uptake by platelets. Alternatively, concentrations of 5-HT in blood and plasma may not be indicative of 5-HT concentrations in local microenvironments surrounding pulmonary epithelial cells and arterial smooth muscle cells. Hyperplasia of pulmonary artery smooth muscle is a hallmark pathological feature of PPH.\textsuperscript{5} The mitogenic effect of 5-HT on pulmonary artery smooth muscle is blocked by 5-HT uptake inhibitors such as fluoxetine,\textsuperscript{34} demonstrating the involvement of SERT sites in this action. It seems possible that SERT substrates other than 5-HT might also be mitogenic. For example, fenfluramine could conceivably be transported into the smooth muscle cells and produce the same effect as 5-HT.

The accumulation of certain medications in arterial smooth muscle cells could trigger mitogenesis through other mechanisms, such as inhibition of K\textsuperscript{+} channels.\textsuperscript{14} This effect requires drug concentrations 10-fold greater than the drug concentrations expected after therapeutic doses. Thus the role of SERT sites might be to translocate drug molecules into pulmonary cells, providing a mechanism to concentrate drugs to a level where K\textsuperscript{+} channel blockade might occur. Perhaps the role of SERT in the pathogenesis of PPH is to serve as a “gateway” for the accumulation and concentration of medications in pulmonary cells. In fact, such data exist for chlorphentermine, which is accumulated in lung and other tissues.\textsuperscript{35,36} Depending on the degree of retention by the lung, time retained, intrinsic drug toxicity, and individual susceptibility, which may have a genetic component,\textsuperscript{37} pulmonary hypertension might develop as a toxic response to these medications or a metabolite.

It is noteworthy that fenfluramine and d-fenfluramine cause depletion of brain 5-HT and apparent loss of 5-HT nerve terminals.\textsuperscript{13} The deleterious effects of these drugs are blocked by pretreatment with 5-HT uptake inhibitors, indicating involvement of SERTs. On the other hand, not all SERT substrates are necessarily detrimental to cells. For example, substrate-type 5-HT–releasing agents have been identified that do not deplete brain 5-HT\textsuperscript{38}; m-chlorophenylpiperazine is one such compound. This drug, a major metabolite of the antidepressant trazodone, increases...
extracellular 5-HT by a SERT-mediated process yet does not 39–41 cause long-term 5-HT depletion. Moreover, trazodone has not been associated with PPH. Taken together, these findings suggest that it will be possible to develop medications that are SERT substrates devoid of hazardous side effects. Such medications would have therapeutic application in the treatment of obesity, addictive disorders, and depression.

Note added in proof: Our “gateway” hypothesis predicts that antidepressants with high affinity for the SERT should reduce the risk of developing fenfluramine-associated PPH. Consistent with this prediction, Abenhaim et al40 reported that the use of antidepressants actually lowered the odds ratio for developing PPH in the case patients.

References


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