**Therapeutic Drug Monitoring Publish Ahead of Print**
**DOI: 10.1097/FTD.0000000000000660**

# Short communication: Distribution of psychotropic drugs into lipoproteins

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**Conflicts of Interests**

The authors declare that there are no conflicts of interests.

## Abstract

**AIM**: The aim of this pilot study was to investigate whether psychotropic drugs frequently analyzed in a routine therapeutic drug monitoring (TDM) laboratory bind to low density lipoproteins/very low-density lipoproteins (LDL/VLDL) in human serum.

**METHODS**: Drug concentrations in 20 serum sample pools containing one psychotropic drug each, and in the LDL/VLDL fractions extracted from the same samples, were measured by triple quadrupole liquid chromatography tandem mass spectrometry (LC-MS/MS). The membrane permeability of the drugs was measured using a *Parallel Artificial Membrane Permeability Assay* (PAMPA).

**RESULTS**: Out of the 20 antidepressants, antipsychotics and antiepileptics examined, seven drugs were detected in both the pooled serum samples and in the LDL/VLDL fraction. Binding of drugs to LDL/VLDL significantly correlated with high octanol:water partition coefficient (logP), high degree of protein binding (PB) and a low polar surface area (PSA). The drugs found in LDL/VLDL, with the exception of aripiprazole, were also characterized by high or intermediate membrane permeability.

**CONCLUSIONS**: The present results indicate that psychotropic drugs with certain characteristics bind to LDL/VLDL in blood. This further implies that lipoproteins could play an important role in drug transport.



**KEYWORDS**: Lipoproteins, psychotropic drugs, therapeutic drug monitoring (TDM), membrane permeability

## Introduction

In pharmacology, the currently accepted dogma is that drugs are transported in the blood either bound to proteins or in an unbound form, and that only the latter is able to exert the desired effect by, for instance, penetrating the endothelium to reach the target cells. In therapeutic drug monitoring (TDM), the total amount of drug in blood, i.e. the sum of protein-bound and unbound substance, is most commonly measured.

During the past decades, scattered studies have indicated that psychotropic drugs may not only bind to the traditional drug transport proteins (albumin, α-1-acid glycoprotein), but also to lipoproteins.[1-11] Recent preclinical experiments showed that antiplatelet and antiarrhythmic agents can bind to LDL/VLDL, which influences the pharmacokinetics of these drugs, partly due to LDL receptor-mediated uptake of lipoprotein-bound drugs into hepatocytes.[12] This was described as a fundamental new concept in pharmacokinetics.

Psychotropic drugs are frequently prescribed due to a high prevalence of psychiatric diseases, but are associated with interactions and metabolic adverse effects (e.g. weight gain, cardiovascular disease).[13, 14] Furthermore, several antipsychotic agents, such as quetiapine, olanzapine and clozapine, have been shown to increase the risk of hyperlipidemia.[15] A potential association with lipoproteins is therefore of particular interest with regard to psychotropic drugs. In theory, such drugs can potentiate their own delivery to target tissues through their lipogenic adverse effects.

The main physiological role of lipoproteins is to transport lipids such as cholesterol and triglycerides through the hydrophilic environment of the circulatory system. Lipoproteins are classified based on their density, from the lowest density, the chylomicrons, to very low density lipoproteins (VLDL), low density lipoproteins (LDL) and finally high density lipoproteins (HDL). In addition to being the main transporters of lipids in the blood,

lipoproteins can also carry certain lipophilic compounds such as fat-soluble vitamins and xenobiotics like endocrine-disrupting chemicals.[16-18]

In this pilot study, we selected a group of psychotropic drugs frequently analyzed in our routine TDM laboratory to examine distribution to LDL/VLDL. Drug concentrations were measured in pooled serum samples, and in isolated LDL/VLDL fractions from the same samples. To further investigate possible mechanisms for drug-lipoprotein association, we measured if the drugs could cross biological membranes using a *Parallel Artificial Membrane Permeability Assay* (PAMPA) kit. The results were correlated with the physico-chemical properties of the drugs to reveal potential characteristics of molecules found in the lipoprotein fraction.

## Materials and Methods

### LDL/VLDL ISOLATION

By the use of our own in-house data on drugs, which are monitored by TDM, we identified 20 of the most frequently analyzed drugs (antiepileptics, antipsychotics and antidepressants). TDM serum samples no longer eligible for routine analysis (i.e. after 1 week storage for potential reanalysis) containing the drug in question were pooled to achieve the sufficient sample volume for LDL/VLDL extraction (2 mL). One pool was created for each drug. The LDL/VLDL-fraction was extracted from the pooled samples using an LDL/VLDL Purification Kit (Cell Biolabs, San Diego, CA, USA), according to the manufacturer's instructions. Briefly, LDL/VLDL were precipitated by adding dextran, which was subsequently removed by several washing steps. In order to confirm VLDL/LDL isolation and absence of serum proteins, LDL content was measured in six randomly selected samples,

and albumin in eight samples using photometry (Roche method ACN 8552, Instrument: Cobas c702, Roche, Basel, Switzerland).

**DRUG MEASUREMENTS**

Samples for drug measurements were prepared by protein precipitation using a Hamilton STARlet (Hamilton Robotics, Martinsried, Germany) and analyzed on an Agilent Technologies 6490 triple quadrupole liquid chromatography tandem mass spectrometry (LC-MS/MS) operated at positive electrospray ionization and a 1290 Infinity LC-system (Agilent Technologies, Waldbronn, Germany). Calibrator sets (MassTox Antidepressants 1, Neuroleptics 1 and Neuroleptics 2) were supplied from Chromsystems (Chromsystems Instruments & Chemicals GmbH, Gräfelfing, Germany). The method was validated according to ISO 15189.[19] The coefficient of variation (CV) for the respective analytes was in the range of 3.06 % to 6.69 % with an average of 4.13 %. The PAMPA-samples were analyzed, after dilution to fit within the standard curve, by LC-MS/MS using a Sciex QTRAP $6500^{+}$ (Sciex, Concord, ON, Canada).

**PARALLEL ARTIFICIAL MEMBRANE PERMEABILITY ASSAY (PAMPA)**

Compound solutions were prepared by diluting 20 mM of drug stock solutions [in dimethyl sulfoxide (DMSO)] in phosphate buffered saline (PBS) (pH 7.4) to a final concentration of 50 μM. Passive diffusion across an artificial membrane was measured using the PAMPA kit from Corning Gentest (Bedford, MA, USA), according to the manufacturer's instructions. In summary, a 96-well filter plate, pre-coated with lipids, was used as the permeation acceptor and a matching 96-well receiver plate was used as the permeation donor. To confirm the integrity of the membrane separating the donor wells from the acceptor wells, we used doxorubicin as an impermeable control substance, and chlorpromazine as a highly permeable substance. After five hours of incubation, the concentrations in the donor and acceptor wells

were measured and the membrane permeability calculated. The membrane permeability is measured in centimeters per second and presented as logarithmic values (Log $P_e$). Based on this parameter, the following categorization of permeability has been suggested: High (> −5.33), intermediate (> −5.66 and < −5.33), low (> −6.14 and < −5.66) and impermeable (←6.14).[20] The pH value in the donor wells was measured using a photometric method on a Beckman Coulter AU680 (Bekman Coulter, Brea, CA, USA).

**CALCULATIONS**

All physico-chemical parameters [octanol:water partition coefficient (logP), polar surface area (PSA), protein binding (PB)] and logarithmic acid dissociation constant (pKa) were extracted from Drug Bank.[21] Because of lack of data, the PB of levomepromazine was assumed to be the same as alimemazine, based on structural similarities. The compatibility factor (CF), as presented in a paper regarding gel separator tubes,[22] for each drug was calculated using the following formula:

$$CF = ((logP)^2*PB)/PSA \qquad \text{(eq. 1)}$$

The ratio between the concentration measured in the LDL/VLDL fractions and the concentration measured in the initial serum pools (L/S-ratio) was also estimated for each drug.

Regarding the PAMPA results, the permeability (cm/s) of the compounds were calculated using the following formula:

$$P_e = \{-\ln[1-C_A(t)/C_{eq}]\}/[A*(1/V_D+1/V_A)*t] \quad \text{(eq. 2)}$$

where A = filter area (0.3 $cm^2$), $V_D$ = donor well volume (0.3 mL), $V_A$ = acceptor well volume (0.2 mL), t = incubation time (seconds), $C_A(t)$ = compound concentration in acceptor well at time t, $C_D(t)$ = compound concentration in donor well at time t, and

$$C_{eq} = [C_D(t)*V_D+C_A(t)*V_A]/(V_D+V_A) \qquad \text{(eq. 3)}$$

## STATISTICS

All statistical analyses were conducted using IBM SPSS statistics for Apple ver. 25 (IBM, Armonk, NY, USA). A p value < 0.05 was required to achieve a statistical significance. To investigate whether logP, PB, PSA or CF was correlated with the presence of drugs in lipoproteins or not, we performed a nonparametric Mann-Whitney U test, with the null hypotheses that the distribution of logP, PB, PSA and CF of the drugs included in the study was equal in the drugs found in lipoproteins as for those not present in lipoproteins. To investigate the impact the three independent parameters have on lipoprotein association, a ternary plot was created, using the SigmaPlot software ver. 9.0 (Systat Software, San Jose, CA, USA).

## ETHICS

The study was performed using disposable, pooled TDM samples, with no possibility of identifying the individual patients.

# Results and Discussion

Successful purification of LDL/VLDL was confirmed by measurements of LDL and albumin in randomly selected samples after LDL/VLDL fractionation. In these LDL/VLDL fractions, high concentrations of LDL (14.2-17.8 mmol/L) and albumin concentrations below the detection limit (2 g/L) were found (data not shown).

Out of the 20 antidepressants, antipsychotics and antiepileptics examined, seven drugs were detected both in the pooled serum samples and in the LDL/VLDL fraction extracted from the same samples (Table 1). Four were antidepressants (sertraline, amitriptyline, fluoxetine and paroxetine) and three were antipsychotics (levomepromazine, aripiprazole and clozapine). Mean concentrations in the serum pools and in the LDL/VLDL fractions, respectively, were

(nmol/L): sertraline: 281/428, amitriptyline: 245/30, fluoxetine: 487/193, paroxetine: 168/24, levomepromazine: 10/3, aripiprazole: 245/30, clozapine: 2342/94. None of the antiepileptic agents were present in LDL/VLDL.

The concentrations in the LDL/VLDL fractions suggest that for some agents, a significant proportion may be associated with LDL/VLDL particles *in vivo*. Interestingly, sertraline was found in a higher concentration in the LDL/VLDL fractions than in the respective serum pools. For all seven substances detected in the LDL/VLDL fractions, we observed a tendency towards a higher logP with higher ratios between the concentrations in LDL/VLDL and serum (L/S ratio, Table 1).

By further examining the influence of the drugs' physico-chemical properties, we found that association of drugs with LDL/VLDL significantly correlated with high logP value, high degree of protein binding, and a low polar surface area (Figure 1A-D, Mann-Whitney U test: $p < 0.001$). We therefore plotted the values of the three physico-chemical parameters of each drug analyzed into a ternary plot to see if the drugs associated with the lipoproteins had similar properties, i.e. if the contribution of each physico-chemical parameter was similar for each drug (Figure 1E). In this plot, we noticed a clear cluster of drugs associated with LDL/VLDL, where the strongest determining factor was high logP, and low PSA. The impact of protein binding was less evident. These findings connect with an intuitive assumption: That substances with low polarity and highly fat solubility are prone to associate with lipoproteins when present in blood. The drugs not associated with the lipoproteins were scattered throughout the plot, and no common characteristic could be found for these. Haloperidol, which shares the criteria of the drugs detected in the LDL/VLDL fraction, was not detected in lipoproteins. However, the reference range for haloperidol is low compared to the other psychotropic drugs. It might therefore be that the drug is below the detection limit in lipoproteins, due to the low total concentration in the blood.

The compatibility factor (CF, eq. 1) has been suggested as an indicator for determining whether a drug would bind to the lipophilic gel in gel separator tubes.[22] According to our results, the CF also correlated with high lipoprotein association, as expected since the CF is a function of the three physico-chemical parameters mentioned above. However, it is noteworthy that in the equation for CF, the value of logP is squared. As a consequence, a positive and negative logP will yield the same value, contributing equally to the CF value. This factor can thus only be used if all the drugs to be compared have a logP value above zero. As seen from Table 1, one of our drugs had a negative logP (levetiracetam; logP = -0.60), and the CF may not to be a fully adequate predictor in determining drug association to lipoproteins.

According to the classification detailed in the "Materials and Methods" section, PAMPA results demonstrated that six of the seven drugs found in LDL/VLDL had a high or intermediate membrane permeability, while aripiprazole came out as impermeable in our study (Table 1). One might suspect that aripiprazole did not permeate the membrane because it was present in an ionized form. We therefore measured the pH value in the donor wells, which was close to 7.4 in all wells (data not shown). This is close to the pKa for aripiprazole (7.46). However, the pKa value of quetiapine (7.06) and clozapine (7.5) also lie close to this value, and both of these substances were found to be highly permeable. The pH value in the donor wells therefore cannot explain the impermeability of aripiprazole. Another explanation could be that aripiprazole is trapped in the membrane, hinting that its association with lipoprotein is in the phospholipid layer, rather than the triglyceride and cholesterol containing core. This could not be determined by means of the PAMPA assay.

In a previous report, the permeability of four of the drugs included in the present study (clozapine, fluoxetine, paroxetine and amitriptyline) was examined.[23] While the exact $LogP_e$

values calculated by us deviate somewhat from these findings, all drugs fell into the same suggested permeation categories (high or intermediate).

With regard to limitations, the samples used in this study had been stored for seven days at 4°C before LDL/VLDL fractionation and drug analysis. This may have influenced how drugs distribute to LDL/VLDL. Furthermore, we have no information about the patients' medical history, or the sampling circumstances. However, the serum pool drug concentrations were all within the respective reference ranges common in standardized TDM. Furthermore, in order to be able to compare 20 drugs, the number of biological replicates was limited to one. In future experiments, the number of parallels should be significantly increased to strengthen the basis of the conclusions.

## Conclusions

In this pilot study, we showed that several psychotropic drugs are associated with LDL/VLDL isolated from human serum. Our results support the model suggested by Yamamoto et al., with total measured drug concentrations representing the sum of not only free and protein-bound drug, but the sum of free, protein-bound and lipoprotein-bound drug.[12]

The drugs found in LDL/VLDL were all characterized by a high logP value, high degree of protein binding, and a low polar surface area. With the exception of aripiprazole, they were also characterized by high or intermediate membrane permeability.

The association of drugs with lipoproteins may have wide-ranging consequences. It has been suggested that lipoprotein-associated drug transport should be distinguished from protein-bound transport due to the ability of lipoproteins to be transferred into tissues and cells through receptor-mediated endocytosis.[12] Our study supports this concept.

If drugs follow lipoproteins into relevant tissues, they may reach a higher tissue concentration than assumed based on the size of the free fraction in blood, with implications for effect and side effect profiles alike. This implies that the concentration of LDL and VLDL in blood could be of importance for the tissue concentration of drugs. Furthermore, co-administration of statins, shown to increase the expression of LDL receptors,[24] may potentially influence the biodistribution and effect of a drug associated to lipoproteins.

Further research is needed to evaluate whether distribution into VLDL/LDL affects the cellular uptake of psychotropic drugs, and which pharmacological and/or clinical consequences this may have. Importantly, revealing the details of distribution of lipophilic drugs to lipoproteins may also contribute to the development of artificial lipoproteins for targeted delivery of pharmacological agents.[25, 26]


## Acknowledgments

We would like to thank the medical laboratory and scientific staff at the Department of Medical Biochemistry and Pharmacology at Haukeland University Hospital and Centre for Pharmacy at the University of Bergen for excellent technical contributions; In particular Kjell Ove Fossan, Kjersti Carstensen and Reidun Æsøy,


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## Figure Legend

Figure 1. Relationship between different physico-chemical properties of drugs and their ability to associate with lipoproteins. A-D: The drugs were classified as either found in lipoproteins, or ***not*** found in lipoproteins, and histograms created based on the frequency (number) of the drugs at the following physico-chemical properties: Polar surface area (A), Protein Binding (B), logP (C), and Compatibility factor (logarithmic) (logCF). E: Ternary plot showing the influence of polar surface area, protein binding, and logP on the drugs present in the LDL/VLDL fraction (filled circles) or drugs not found in the LDL/VLDL fraction (open circles).

**TABLE 1.** Physico-chemical properties of antidepressants, antipsychotics and antiepileptics, and distribution to LDL/VLDL in human serum.

| | LogP | PB | PSA | CF | Found in LDL | L/S-ratio | $LogP_e$ | Permeation category |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| Antidepressants | | | | | | | | |
| Sertraline | 5.10 | 98 | 12.0 | 212.4 | X | 1.51 | -5.51 | Intermediate |
| Amitriptyline | 4.92 | 97 | 3.2 | 733.8 | X | 0.17 | -5.24 | High |
| Fluoxetine | 4.05 | 95 | 21.3 | 74.2 | X | 0.40 | -5.26 | High |
| Paroxetine | 3.60 | 95 | 39.7 | 30.8 | X | 0.14 | -5.30 | High |
| Escitalopram | 3.50 | 56 | 36.2 | 18.9 | | | | |
| Venlafaxine | 3.20 | 30 | 32.7 | 9.4 | | | | |
| Mirtazapine | 2.90 | 85 | 19.4 | 3.9 | | | | |
| | | | | | | | | |
| Antipsychotics | | | | | | | | |
| Levomepromazine | 4.70 | 90 | 15.7 | 124.3 | X | 0.32 | -5.40 | Intermediate |
| Aripiprazole | 4.50 | 99 | 44.8 | 44.6 | X | 0.13 | -8.83 | Impermeable |
| Haloperidol | 4.30 | 92 | 40.5 | 42.0 | | | | |
| Clozapine | 3.20 | 95 | 30.9 | 31.4 | X | 0.06 | -5.24 | High |
| Quetiapine | 2.80 | 83 | 48.3 | 13.5 | | | | |
| Risperidone | 2.50 | 88 | 61.9 | 8.9 | | | | |
| Olanzapine | 2.00 | 93 | 30.9 | 12.0 | | | | |
| Paliperidone | 1.80 | 74 | 82.2 | 2.9 | | | | |
| Amisulpride | 1.06 | 17 | 101.7 | 0.2 | | | | |
| | | | | | | | | |
| Antiepileptics | | | | | | | | |
| Valproic acid | 2.75 | 90 | 37.3 | 18.2 | | | | |
| Lamotrigine | 2.50 | 55 | 90.7 | 3.8 | | | | |
| Carbamazepine | 2.45 | 76 | 46.3 | 9.9 | | | | |
| Levetiracetam | - 0.60 | 10 | 63.4 | 0 | | | | |
| | | | | | | | | |

Table 1. LDL = low density lipoprotein; VLDL = very low density lipoprotein; logP = partition coefficient; PB = protein binding in percent; PSA = polar surface area; CF (compatibility factor) = ((logP)2*PB)/PSA; L/S-ratio (lipoprotein-drug-ratio) = drug concentration in LDL-VLDL/drug concentration in serum (mean value, amitriptyline: n=2, fluoxetine: n=2, paroxetine: n=3, sertraline: n=2, aripiprazole: n=3, clozapine: n=2, levomepromazine: n=2). LogPe = the logarithmic value of the membrane permeability (cm/s) (mean value: clozapine: n=3, amitriptyline: n=3, paroxetine: n=3, levomepromazine: n=3, aripiprazole: n=3, fluoxetine: n=2, sertraline: n=2). See methods section for information of how the different parameters were collected and calculated.

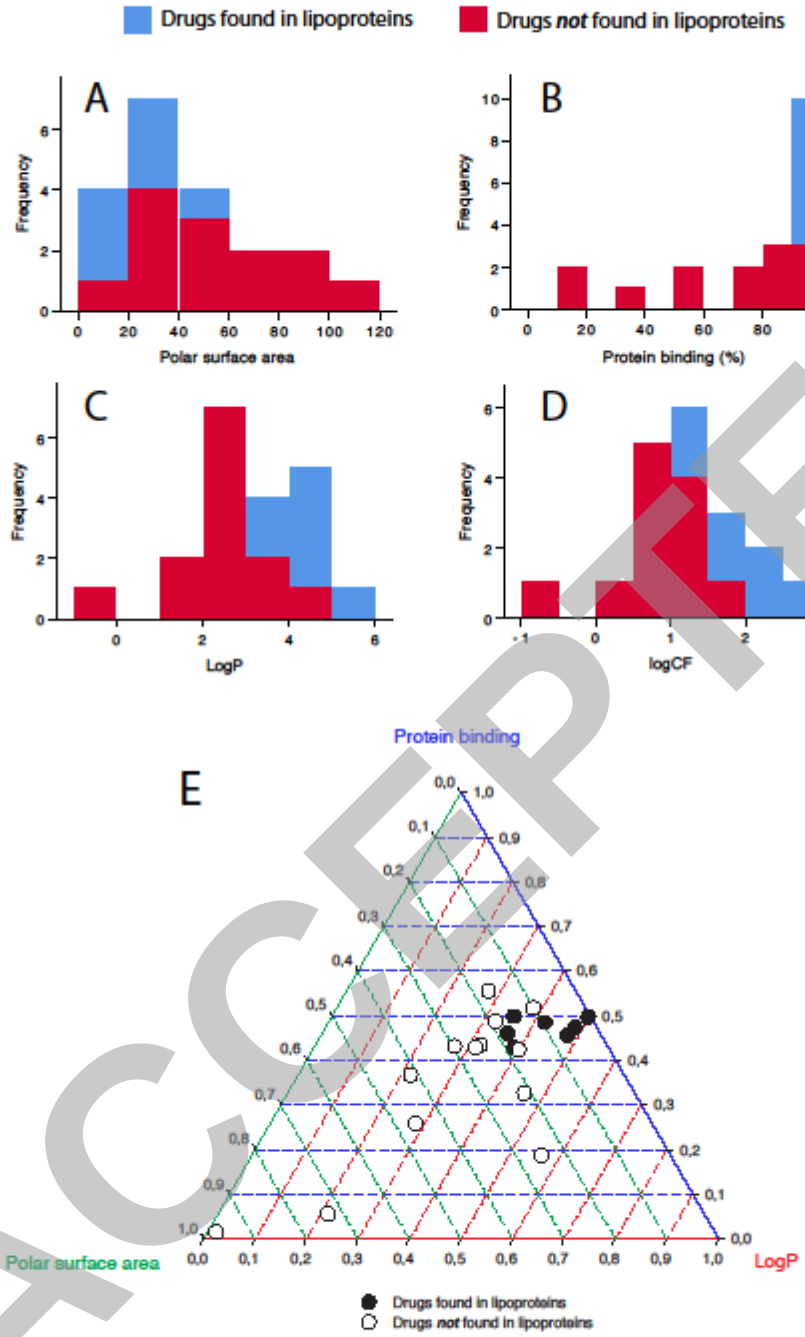




**FIGURE 1**. Relationship between different physico-chemical properties of drugs and their ability to associate with lipoproteins. A-D: The drugs were classified as either found in lipoproteins, or ***not*** found in lipoproteins, and histograms created based on the frequency (number) of the drugs at the following physico-chemical properties: Polar surface area (A), Protein Binding (B), logP (C), and Compatibility factor (logarithmic) (logCF). E: Ternary plot showing the influence of polar surface area, protein binding, and logP on the drugs present in the LDL/VLDL fraction (filled circles) or drugs not found in the LDL/VLDL fraction (open circles).