藥物基因檢測案例討論與現今挑戰

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MANAGING MEDICATIONS FOR THE FRAIL ELDERLY PATIENTS IS A HUGE CHALLENGE....

Mainly due to the concerns of "Polypharmacy"

Clinical CASE report to initiate DRUG SAFETY and MEDICTION USE research

CASE REPORT

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Severe hypertriglyceridemia secondary to venlafaxine use in an older adult on dialysis -case report

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Abstract

Background: Although the prescribing information for Venlafaxine extended release includes a discussion about possible increases in total cholesterol and triglycerides (TG) seen in healthier adult patients during premarketing clinical trials, no post-marketing studies or case reports, that discuss the effects of venlafaxine on TG in elderly patients with chronic kidney disease.

Case presentation: We report a 71 year-old male patient with end-stage renal disease on hemodialysis, with a history of coronary artery disease, mild hyperlipidemia, and hypertension. This patient twice demonstrated the severe rises in triglycerides while taking the antidepressant, *i.e.*, venlafaxine, and discontinuing the long-term use of fenofirate. The adverse drug reaction sub-committee at the hospital rated the second event as a "probable reaction" using the Naranjo nomogram, accordingly.

Conclusions: This case demonstrates the risk of changes in lipid profiles while taking venlafaxine and receiving on and off fenofibrate therapy in the older adult patient with chronic kidney disease and under hemodialysis. Regular monitoring for lipid changes after starting venlafaxine is strongly advised for patients with existing risk factors.

Keywords: Hypertriglyceridemia, Hemodialysis, Venlafaxine, Older Adult, Case report

Severe Hypertriglyceridemia Secondary to Venlafaxine Use in an Elderly Dialysis Patient-case report
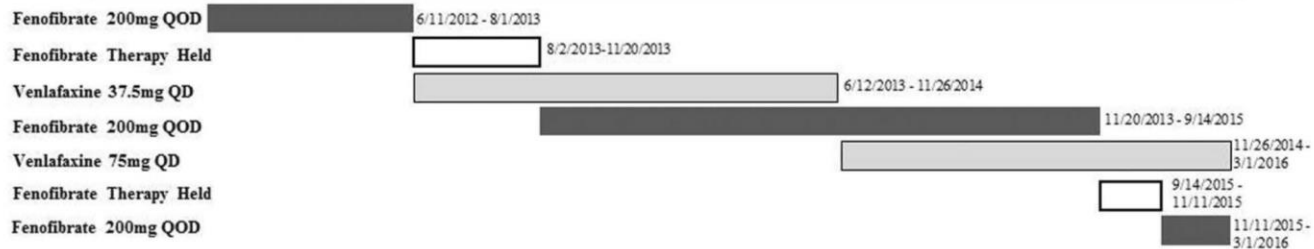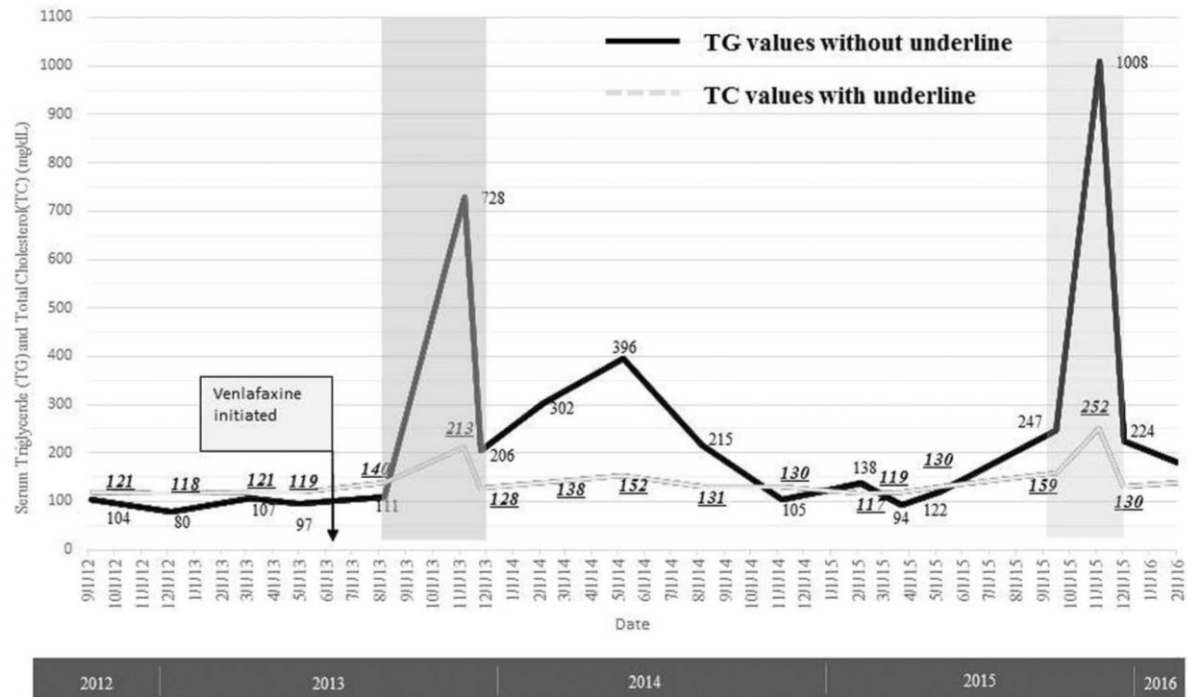

Fig. 1 Serum triglycerides and periods without finofibrate therapy and timeline of fenofibrate and venlafaxine ER use, 2012–2016. Shaded areas mark time when patient was not prescribed finofibrate. Serum triglyceride in mg/dL to mmol/L, x0.01129

Prior to venlafaxine, *mirtazapine and escitalopram* were initiated and **discontinued due to adverse effects of drowsiness and gastrointestinal upset,** respectively.

"The effect of escitalopram was independent of 5-HTT and 5-HTR2a polymorphisms." (Psychiatry Investig 2016;13(1):157-160)
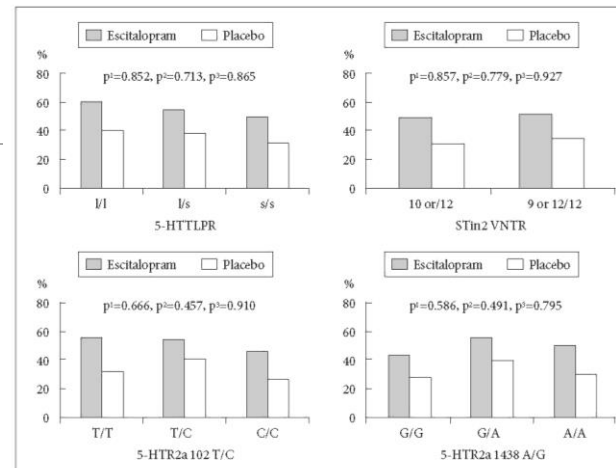
Figure 1. Hamilton Depression Rating Scale remission rates by treatment groups and genotypes. 5-HTTLPR: serotonin transporter gene linked promoter region, STin2 VNTR: serotonin transporter intron 2 variable number tandem repeat, 5-HTR2a: serotonin 2a receptor, p^1: values for remission status in escitalopram group, p^2: values for remission status in placebo group, p^3: values for interaction between treatment groups and genotypes.

158 Psychiatry Investig 2016;13(1):157-160

Afterward, this elderly patient further encountered either thrombosis (i.e., angina) or bleeding (i.e., gastrointestinal bleeding) alternatively several times…

Further PGx Testing to facilitate medication use

This patient was also vulnerable to the concerns of thrombosis, bleeding and psychotropic agents afterward. With his permission to collect saliva samples to send to the certified laboratory for PGx testing, his corresponding gene panel, e.g., CYP2D6, CYP2C19, CYP3A4, VKORC1, OPRM1, HTR2A, associated with medications' metabolisms, transports and targets, were examined comprehensively.

Current medication when taking PGx Testing

Name	quantity	dosage	frequency	route	time
Thalidomide 50mg/Cap	1	TB	QW	PO	PC
Isosorbide-5-mononitrate 20mg/Tab	1	TB	BID	PO	PC
FENOFIBRATE 200mg/Cap	1	TB	Q3D	PO	PC
Ultracet (Tramadol / acetaminophen)Tab (複方)	0.5	TB	BID	PO	PC
Bisacodyl(錠劑) 5mg/Tab	2	TB	HS	PO	AC
Clopidogrel 75mg/Tab	1	TB	QD	PO	PC
Nifedipine OROS 30mg/Tab	1	TB	BID	PO	PC
Valsartan 160mg/Tab	0.5	TB	QD	PO	PC
Rabeprazole 20mg/Tab	1	TB	QD	PO	AC
Quetiapine 100mg/Tab	0.5	TB	HS	PO	PC
VENLAFAXINE HCl 75mg/Cap	1	TB	QD	PC	PC
Darbepoetin Alfa 20mcg/0.5mL/Syringe	1	AM	STAT	1	SC

Rabeprazole is therefore the PPI least affected by CYP4502C19 genetic polymorphism.

PGx testing findings

Test:	Phenotype:	Genotype:
CYP2D6	Normal Metabolizer	*1/*2A
CYP2C19	Intermediate Metabolizer	*1/*2
CYP2C9	Normal Metabolizer	*1/*1
CYP3A4	Normal Metabolizer	*1/*1
CYP3A5	Poor Metabolizer	*3/*3
VKORC1	High Sensitivity	c.-1639G>A AA
HLA-B*57:01	Negative	*57:01-rs2395029T>G TT
SLCO1B1	Normal Function	*1B/*1B
UGT1A1	Normal Metabolizer	*1/*1
TPMT	Intermediate Metabolizer	*1/*3C
DPYD (DPD)	Normal Metabolizer	*1/*1
IFNL3 (IL28B)	Favorable Response	rs12979860C>T CC
NAT2	Intermediate Acetylator	*4/*7B
F2 (Factor II)	Negative	c.*97G>A GG
F5 (Factor V) Leiden	Negative	c.1601G>A GG
MTHFR	Intermediate Activity	c.665C>T CT / c.1286A>C AA
CYP2B6	Normal Metabolizer	*1/*1
OPRM1	High Sensitivity	c.118A>G AA
HTR2A	Normal Activity	c.-998G>A AA
HTR2A	Unfavorable Response	c.614-2211T>C CC
HTR2C	Decreased Risk	c.-759C>T TT
GRIK4	Favorable Response	c.83-10039T>C CC
CYP1A2	Normal Metabolizer	*1A/*1A
COMT	High Activity	c.472G>A GG
ADRA2A	Intermediate Response	c.-1252G>C GC

Laboratory results interpretation (I)

CYP2C9 (genotype *1/*1) normal activity

CYP2C19 Intermediate metabolizers (genotype *1/*2): decreased CYP2C19 activity

- ◦ CYP2C19 inactivated drugs: need to decrease doses to prevent adverse effects
- ◦ Prodrug being activated by CYP2C9: need to increase dose or change medication

CYP3A5 Poor metabolizers (non-expressers): greatly decreased CYP3A5 activity; majority of population→ standard dosing

VKORC1 (genotype AA) high sensitivity: decreased VKORC1 activity and need to adjust warfarin initial dose as the following

Table 1.

The FDA (2017) Drug Label for Warfarin. Three Ranges of Expected Maintenance Warfarin Doses based on CYP2C9 and VKORC1 Genotype.

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5–7 mg	5–7 mg	3–4 mg	3–4 mg	3–4 mg	0.5–2 mg
AG	5–7mg	3–4 mg	3–4 mg	3–4 mg	0.5–2 mg	0.5–2 mg
AA	3–4 mg	3–4 mg	0.5–2 mg	0.5–2 mg	0.5–2 mg	0.5–2 mg

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Laboratory results interpretation (II)

NAT2 intermediate acetylators: decreased N-actyltransferase (NAT2) activity, increase drug levels and risk for adverse effects

F2 (Factor II) negative: normal factor II levels and no increased risk of thrombosis

OPRM1 high sensitivity: …..

Drug-gene interaction findings

DRUG-GENE INTERACTIONS

| Impact	Medication	Cause(s)	Effects & Management
🛑 MAJOR	clopidogrel	CYP2C19 Intermediate Metabolizer	• Clopidogrel active metabolite levels may decrease by 31-50%. • Decreased effectiveness of clopidogrel in CYP2C19 Intermediate Metabolizer patients. • Increased risk of major adverse cardiovascular events and stent thrombosis. • Avoid clopidogrel in CYP2C19 Intermediate Metabolizer patients. • These recommendations apply predominantly to ACS patients undergoing PCI. • Potential alternatives to clopidogrel include: ticagrelor (Brilinta) and prasugrel (Effient).
⊖ MINOR	venlafaxine	CYP2C19 Intermediate Metabolizer	• Venlafaxine levels may increase by 26-75%. • Increased risk of dry mouth, sexual dysfunction, hypertension, nausea and insomnia. • Decrease venlafaxine dose if necessary in CYP2C19 Intermediate Metabolizer patients. • Potential alternatives to venlafaxine include: levomilnacipran (Fetzima) and desvenlafaxine (Pristiq).

這個藥物基因檢測適合這個病人嗎？

Factors to consider the labs or testing

Logistics

Total cost

Genes and variants

- Reporting of results
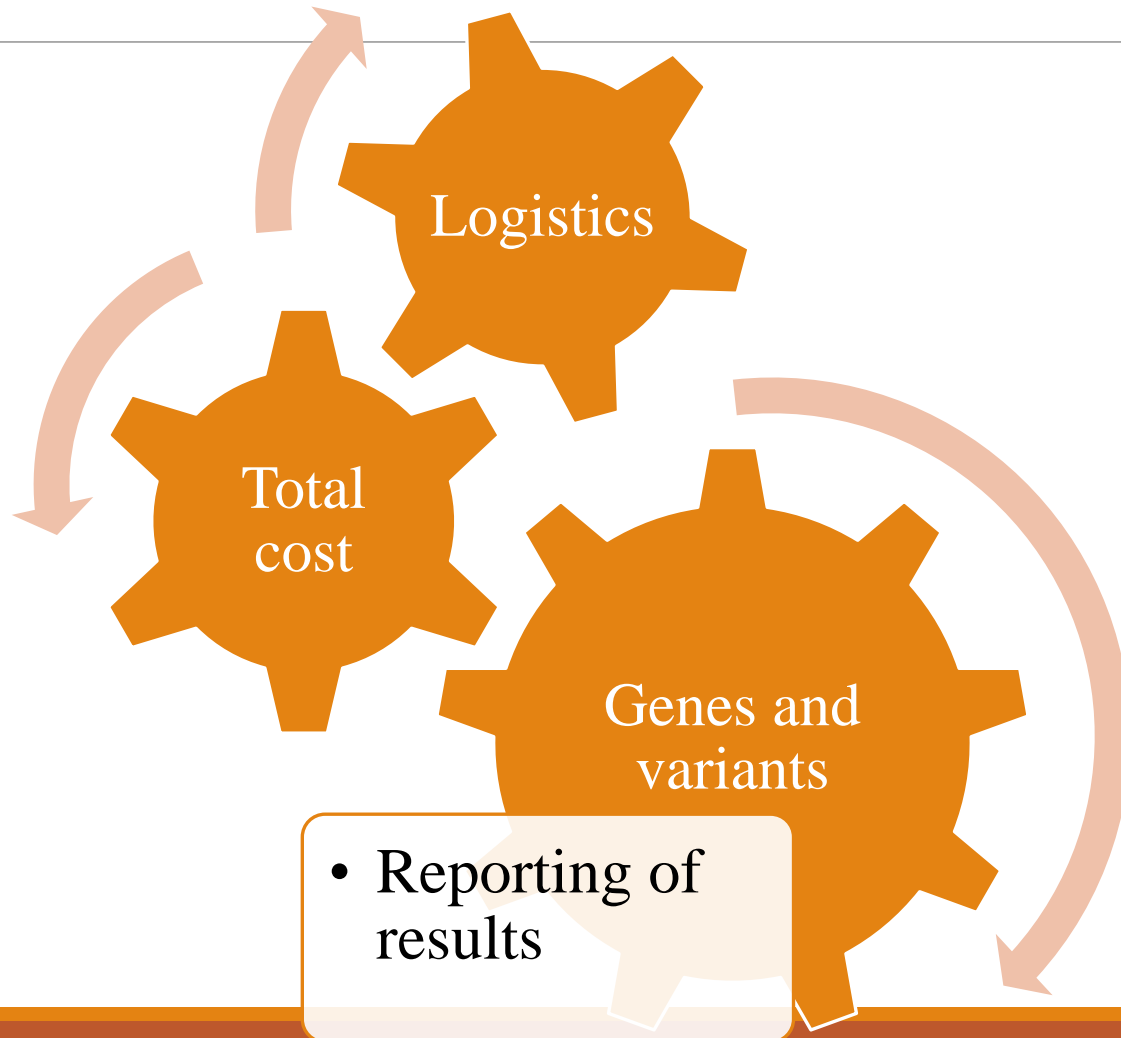
Which lab or testing is the best for the patient?

	PGX1	PGX2	PGX3	PGX4	PGX5
# of gene	22	21	16	14	10
# of variant covered	90	88	64	56	26
# of CPIC gene	6	10	5	6	4
# of CPIC variants covered	48	70	32	36	18
Cost	449	249	399	349	149

Variant selection

Gene	PGX1	PGX2	PGX3	PGX4	PGX5
CYP2C19	*2,*3,*4,*4B,*10,*17	*2,*3,*4,*4B,*5,*6,*7,*8,*9,*10,*17	*2,*3,*4,*5,*7,*8,*17	*2,*3,*4,*6,*8,*9,*17	*2,*3,*17
CYP2C9	*2,*3,*4,*5,*6,*11,*18	*2,*3,*4,*5,*6,*11,*27	*2,*3,*4,*5,*6,	*2,*3,*4,*5,*6,*11,*12	-
CYP2D6	*2,*3,*4,*5,*6,*11,*18	*2,*3,*4,*4M,*5,*6,*7,*8,*9,*10,*11	*2,*3,*4,*5,*6,*7,*8,*9,*10,*11,*12,*14A,*17,*29,*35,*41,*56A…	*2,*3,*4,*5,*6,*7,*8,*9,*10,*11,*12,*14A,*17,*41,…	*2,*3,*4,*5,*6,*9,*10,*11,*41,…
CYP3A5	*3,*6,*7	*1D,*3,*3C,*6,*7	*2,*3,*7	-	*3,*6,*7

Variant frequency differ from population to population

CYP2C19 allele	East Asian Allele Frequency	South/Central Asian Allele Frequency	Caucasian Allele frequency (European & North American)	African American Allele frequency	American Allele frequency
*1	57.60	48.50	62.10	57.00	67/00
*2	29.30	33.10	14.60	18.30	13.10
*3	8.60	1.60	0.60	0.30	0.30
*4A	0.10	0.00	0.30	0.00	0.03
*5	0.00	0.00	0.00	0.00	0.00
*6	0.00	0.00	0.10	0.00	0.00
*7	0.00	0.00	0.00	0.00	0.00
*8	0.00	0.00	0.30	0.20	0.10
*9	0.00		0.00	1.10	0.10
*10	0.00		0.00	0.40	0.10
*12	0.00		0.00	0.20	0.00
*13	0.00		0.10	1.20	0.40
*14	0.00		0.00	0.00	0.00
*15	0.20		0.20	1.40	0.40
*17	1.60		21.30	20.10	16.30
*35	0.00		0.00	0.80	2.10

Different PGx testing has different coverage… Take 2C19 as the example

Gene	PGX1	PGX2	PGX3	PGX4	PGX5
CYP2C19	*2,*3,*4,*4B,*10,*17	*2,*3,*4,*4B,*5,*6,*7,*8,*9,*10,*17	*2,*3,*4,*5,*7,*8,*17	*2,*3,*4,*6,*8,*9,*17	*2,*3,*17

Which one is better?

Other case practice

AC is a 47 yo Caucasian male enrolled in his employer's executive health program. AC is relatively healthy. He currently takes atorvastatin (Lipitor) for high cholesterol and ibuprofen (Advil) for persistent back pain (uncontrolled), related to a previous sports-related injury. His father (Caucasian/European) has been diagnosed with skin cancer and his mother (Ashkenazi Jewish) has a significant family history of heart disease.

Gene	Genotype		Result
CYP2D6	*4/*17	PM IM NM RM UM	**Poor to Intermediate** Decreased activity. Drugs converted to active metabolite(s) may have reduced efficacy. Active drugs converted to inactive metabolite(s) may cause side effects or toxicity.
CYP2C19	*4B/*4B	PM IM NM RM UM	**Poor** No to very low activity. Drugs converted to active metabolite(s) may have reduced efficacy. Active drugs converted to inactive metabolite(s) may cause side effects or toxicity.
UGT1A1	*1/*6	⚠	**Increased Risk** Decreased UGT1A1 activity. Increased risk for severe neutropenia with irinotecan and toxicity and hyperbilirubinemia with nilotinib. Consult drug labeling for dosing recommendations. Genotype also indicates carrier status for Gilbert syndrome, but is not expected to cause marked congenital unconjugated hyperbilirubinemia.

藥物基因檢測現今挑戰

個人化醫療的夢想與挑戰 https://scitechvista.nat.gov.tw/c/sVr1.htm

醫師也可以憑借著檢測產品的協助，在出現症狀後，依據個人不同的體質，設計出個人化的醫療療程而朝向「個人化醫療」的理想邁進。如同分子生物科學的研究為人類帶來了生技藥物的新產品概念，基因科技也為醫療應用開啟了全新的未來，新科技、新技術所創造出新式的分子檢測產品，或許未來只需個體的一滴血就可以快速檢測出病患的健康狀態，甚至得知個體、疾病與不同藥物之間的龐大資訊。

量身打造 個人化用藥
https://ejournal.stpi.narl.org.tw/sd/download?source=10401-03.pdf&vlId=F267F8EB-842F-4229-9031-8D2147337B1C&nd=1&ds=1

"研究人員在面對龐大的基因資訊時，如何利用統計的方式找出疾病與基因之間的關聯性，仍需要有功能強大的生物資訊 軟體協助分析，包含資料庫的建立、模擬 關聯性演算法的發展、電腦新藥設計輔助與診斷分析產品開發等技術的進步，也是 未來運用藥物基因體學時必須面臨的挑戰。","法規與倫理因素是這領域的最大 挑戰，基因隱私權的維護、保險制度可能面 臨的改變，與醫療人員的訓練，都是藥物基 因體學或個人化醫療未來發展的關鍵。"

個人化醫療的夢想與挑戰

2012/06/11 王大維|工業技術研究院產經中心經理

https://scitechvista.nat.gov.tw/c/sVr1.htm

隨著新穎分子生物應用技術以及對人類基因定序的發展(例如使用全基因組晶片檢測或次世代定序法)，預期未來研究將帶領我們朝向發現藥物新標的及個人化醫療前進，以促進藥物治療的效益與安全性比例最大化。

Thank you for your attention

QUESTIONS ARE WELCOME